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PRESIDENTIAL ADDRESS

Pacific Coast Surgical Association

SINCE the founding of the Pacific Coast Surgical Association thirty-six years ago, this society has been privileged to listen to a succession of scholarly Presidential Addresses at its annual meetings. I stand before you today with sincere appreciation of the great honor you have bestowed upon me, but with a humble knowledge of my own inability to offer you a masterful oration or a solution to any of the many problems which confront our world, our nation and our profession. Therefore, with your kind indulgence, I should like to express some of the personal thoughts of one who, after thirty-five years in the practice of medicine, is soon approaching without regret retirement from professional activities.

The world today is involved in two unprecedented revolutions, a scientific and a social revolution. Each of these will increasingly affect the practice of medicine.

Scientific progress has produced a galaxy of new developments in instrumentation: electrophoresis, chromatography, spectrophotography, radioisotopes, the ultracentrifuge, interference microscopy, the electron microscope and a plethora of electronic machines of spectacular value in medical research and in medical treatment. Today the rapidity of accumulation of scientific facts far outstrips true knowledge and understanding. "In every medical library the very walls are bulging with growing masses of undigested and indigestible data."*

The rapid momentum of acquisition of new scientific information has created a belief that the cure and prevention of cancer are just around the corner, that in the very near future not only will all diseases be curable but all will be preventable. There are even those who are inclined to believe that life everlasting will soon be here on earth.

A few months ago Mr. Godfrey, of radio and television fame, having been operated upon himself for cancer, proposed a monetary crash program for quick solution of the problem of cancer. His proposal made headlines on the front pages of newspapers from coast to coast.

On January 16, President Eisenhower proposed a $1,100,000,000 Federal outlay in the year 1962 "to fight cancer, heart disease, mental illness, and other major perils to the nation's health."

Such largesse no doubt will further expand the growing mass of scientific facts. But how much of this high-priced data will truly increase our knowledge of the cause and treatment of disease? I, for one, can share no enthusiasm for the hope that great medical progress is made in such manner.

The second revolution we are witnessing is a social revolution. The heritage of our country was ever the preservation of the individual's right to independence. But the social philosophy of our nation has changed to one of ever increasing control and regimentation of the people by government. Expanding bureaucracy is nurtured by a deliberately designed educational program which has persistently indoctrinated the people with the belief that they have the right to a good job, the right to a good home, the right to a guaranteed income, the right to good health and the right to medical care. They have been taught that it is the

* McCLURE, D. M. Per ardua ad ardua. *Lancet*, 2: 1388, 1960.

responsibility of government to provide these things; and any notion that one must earn these privileges by hard work is archaic.

Of particular concern to us, as doctors, is the effect upon the practice of medicine of the growing belief that good health and good medical care are the right of every individual and that it is the responsibility of government to provide them. The great majority of doctors are of the firm conviction that government controlled medical practice will result in significant deterioration of medical care. Yet there would seem to be an increasing number of doctors, particularly young doctors, embued with the social philosophy of dependence upon government, who are prepared to accept government control of medical practice without qualm.

There is considerable evidence that this new social philosophy has infiltrated the educational program of our medical schools. In many areas there has developed a widening schism between faculty members and practicing physicians. There appears to be, on the one side, a concentrated fascination for the unfolding wonders of science and, on the other side, concern about the training of doctors in the knowledge and understanding necessary to the highest quality of medical service. Healing of this breach is sorely needed for the betterment of medical education and of medical practice.

Regardless of individual political or social philosophy, the medical profession faces a great responsibility in the advocacy of a sound program for the provision of the best possible medical care, attuned to a changing social philosophy but with preservation of the dignity and the individual rights of both patient and doctor.

Concurrently with the scientific and the social revolutions, we have experienced a significant decline in the traditionally honored and respected position of the physician in his community. In continuing crescendo the medical profession has been the target of slurs and innuendos, and of vituperative attacks by politicians and government spokesmen, by the public press and even by courts of law.

The medical profession justifiably resents such abuse, but its ineptness in the fields of public relations and politics has accomplished little in rebuttal of this derogatory attack. Greater accomplishment in these fields is vital to the re-establishment of the public's faith in our profession.

But also, physicians must be alert to criticism, and seriously reflect upon the possible effects on prestige of their own shortcomings.

Traditionally, the individual who undertakes the arduous program of medical training is of humanitarian character, dedicated to the purpose of service to others and administration to the needs of the sick and infirm. Traditionally, the young doctor knows and accepts the oath of Hippocrates, and pledges himself to abide by its precepts. Above all else, it is conformity to these precepts which has earned for physicians the love and respect of all people.

The great majority of doctors today are dedicated to honorable service to humanity. But not all doctors are so dedicated, and deviation from Hippocratic principles by some physicians inevitably results in significant damage to the prestige of the medical profession.

Most blatant are the crimes for which doctors have been convicted in courts of law. In recent times in this immediate vicinity these have included conviction for falsification of income tax returns, for sexual perversion, for drunken driving, for fathering illegitimate children, for narcotics violations, for illegal abortions and even for murder. If it were not for the fact that it might sound somewhat attractive, we might also include the crime commonly referred to as "living in sin."

Having paid the legal penalty for their crimes, the majority of these individual doctors have resumed the practice of medicine. But their conduct has done inestimable harm to the good name of the medical profession.

Among other dishonorable and unethical practices which damage the reputation of our profession are the performance of unnecessary operations, ghost surgery, the prescribing of unnecessary and unwarranted treatment, the charging of exorbitant fees and the padding of bills to insurance companies.

It may well be that the greatest damage of all to public respect for the physician is caused by the careless and thoughtless errors of omission of which many of us may be guilty at one or another time.

An increasing number of doctors are off call over week-ends without provision for emergency medical care for their patients.

All too often a patient is finally seen by his doctor, long after the time of his appointment. This is usually unavoidable and not by design, but a brief word of apology and explanation

would go a long way in soothing the irritation of the patient and the resentment which he directs toward the doctor.

All too often the doctor is remiss in adequate explanation to the patient of the reasons for undertaking necessary diagnostic and therapeutic procedures. He may be even more remiss in similar explanation to an equally concerned close relative of the patient.

Not infrequently the doctor is negligent in adequate explanation to the patient of the operative procedure which he proposes to execute, of the possible risks of the operation, of the anticipated postoperative course, of the probable duration of hospitalization and of the expected period of disability from work.

At times the patient is not informed in advance that his doctor is planning to be away during the patient's postoperative hospital stay, and the patient may then believe he has been abandoned by his own doctor. Not infrequently the details of postoperative care of the patient are left to the intern or resident. The distress and apprehension of the patient following surgical procedures do not always receive sympathetic consideration by the surgeon.

These are but a few of many things which may seem trivial to the busy doctor, but do detract from the patient's respect for his physician.

It should be unnecessary to say that these criticisms are not directed toward the members of this Association. Collectively, this Society has maintained the highest standards of dedication to the purpose of progress in the field of surgery. Individually, each of its members has been carefully selected not only for his achievement in the science of his specialty, but for his position of honor and respect in his community.

Yet we, the members of this Association, should never hold ourselves above criticism, and by self criticism should ever strive to uphold the principles of honorable service in the practice of medicine.

The members of this Association have a great responsibility as preceptors in the training and development of young surgeons. It is not enough to educate these young men in knowledge of disease and diagnosis and in the technic of surgical procedure. There is an equal responsibility to inculcate dedication to conscientious, humanitarian service and to the precepts of the Hippocratic oath.

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Perforated Peptic Ulcer: Results After Simple Surgical Closure

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PERFORATED peptic ulcer still presents an unsolved problem in management. There have been excellent studies of the factors concerned with the treatment of the immediate episode, but relatively little consideration of the future morbidity and mortality after recovery from the perforation.

In an attempt to elucidate some factors which could influence the type of treatment of the acute perforation with improvement not only of the immediate but also of the long term results, a study was made of 362 patients treated consecutively at the Wadsworth General Hospital, Veterans Administration, Los Angeles, during an eight year period. This supplements a report made in 1957 [60].

The only patients considered were those who had free perforations of benign peptic ulcers treated by simple surgical closures. Information was obtained from hospital charts, printed questionnaires and personal interviews. To make the follow-up evaluation more significant, especially since patients with perforated peptic ulcers usually do well for a while after recovery, this study includes only those patients treated before 1956. Most of the follow-up periods are of more than five years duration. In this veteran population, all patients were male except for two. Their ages varied from twenty-one to eighty-two years. The distribution compiled in Table 1 shows that 44 per cent were over fifty years of age and 17 per cent were over sixty. Their ulcers were duodenal in 85 per cent and gastric in 15 per cent.

TABLE I
PATIENTS' AGES

Years	Per cent
20–29	15.4
30–39	24.1
40–49	16.4
50–59	26.7
60–69	13.1
Over 70	4.3

TABLE II
POSTOPERATIVE COMPLICATIONS

Type	Per cent
Related to gastrointestinal tract	30
Wound	30
Pulmonary	22
Cardiac and other	18

Symptoms of peptic ulcer were present preoperatively in 86 per cent, and were of over three years duration in 55 per cent. Manifestations, which were severe in 26 per cent, included hemorrhage in 13 per cent, previous perforation in 4 per cent and some degree of obstruction in 3 per cent. Almost a third of the patients had had some sort of previous medical treatment for ulcer.

The clinical manifestations at the time of perforation were characteristic of the disease.

In the postoperative period eighty-six pa-

TABLE III
IMMEDIATE MORTALITY FACTORS

Factors	Patients (%)	Died (%)
Treatment within 24 hours	90.0	6.0
Treatment after 24 hours	10.0	42.0
Age under 50 years	56.0	2.5
Age over 50 years	44.0	18.5
Bleeding	4.5	37.5
Shock	7.0	50.0
White blood cells under 10,000	12.0	43.0

tients (24 per cent) developed complications. (Table II.) Thirty-four patients died which makes a mortality rate of 9.5 per cent of the entire group. In twenty-eight of these, death can be ascribed directly to the ulcer. In the last five years of this study the mortality rate declined to 7.6 per cent. The rate was markedly influenced by several factors as noted in Table III: the age of the patient, the duration of perforation before treatment, associated bleeding, shock and low leukocyte count. Eighteen of the thirty-four deaths were in patients with subnormal temperatures. Gastric ulcers carried an initial mortality rate of 30 per cent higher than that for duodenal ulcer. In our series the death rate was somewhat lower in the patients with chronic disease.

Of the 328 survivors fifty-one patients (15.5 per cent) had definitive ulcer surgery performed within a few months after recovery because of a history of previous severe disease. Hemorrhage in sixteen patients, obstruction in ten, perforation in four and gastric ulcer suspected of carcinoma in five were among the major indications for surgery.

There were 277 patients discharged on medical therapy and of these, ninety-nine patients were transient veterans who were lost for follow-up study. The results of the evaluations of the 178 cases followed are summarized in Table IV. Of these, eighty-two (46 per cent) are classed as failures. Five died of ulcer disease and sixty-seven required surgery for ulcers producing major complications. Indications for surgery included major hemorrhages in twenty-one patients, recurrent perforations in twelve and obstruction in eleven. Two deaths occurred at the time of this later surgery. An additional ten patients continued to have severe symptoms without receiving another surgical procedure.

TABLE IV
FOLLOW-UP RESULTS

Results	No. of Patients	Per cent
Failures		
Died of ulcer	5	2.8
Required surgery	67	37.6
Severe manifestations	10	5.6
Subtotal	82	46.0
Response to treatment		
Mild moderate symptoms	44	24.7
(with ulcer)	(6)	(3.4)
No symptoms	35	19.7
Died of other disease	17	9.6
Subtotal	96	54.0
Total	178	100

The remaining ninety-six patients are classed as responding to medical therapy. Of forty-four patients with mild to moderate symptoms, six have evidence of active ulceration. Seventeen patients have died of disease unrelated to their ulcers. There are thirty-five patients who remain free of symptoms and without evidence of ulcer.

Figure 1 presents in percentages the results of the follow-up group of 178 cases plus the fifty-one patients who received additional surgery after recovery from their perforations. It

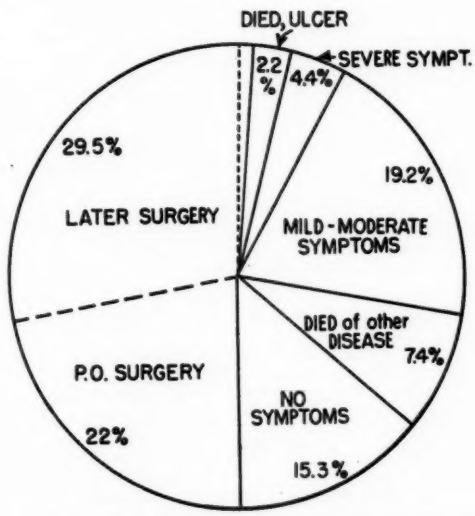

FIG. 1. Results after perforation (229 known survivors).

is evident that over one half (51.5 per cent) of the patients have had ulcer curative surgery performed because of severe disease. Without additional surgery, 2.2 per cent died of ulcer disease and 4.4 per cent were severely disabled with pain. An additional 19.2 per cent have continued to have mild or moderate symptoms of ulceration. There are at least a few more who have had relatively asymptomatic ulcers with potential future complications. The vast majority of these failures had a history of chronic disease with major complications prior to perforation. Most of the patients developed severe manifestations within one year of their initial perforation, although a few did not have a severe recurrence for as long as seven years after perforation. Without evidence of recurrent ulceration, 7.4 per cent have died of another unrelated disease. Finally, the symptom-free group comprises 15.3 per cent of all those followed.

COMMENTS

The over-all mortality from acute perforation of peptic ulcer has shown a decline throughout the years with the progressive improvement in care using modern methods and drugs. For many patients, the immediate results are very good with low morbidity and mortality rates [6,8,12,24,31,42,43,47,49,56,72].

There are three general methods of management. The first method, simple surgical closure of the perforation, has been universally the most popular since its introduction by Mikulicz in 1880 with early successes reported by van Heusner in 1892 and by Dean in 1894 [1,7,11,-20,27,30,31,40,47,54,67,71]. The second method, gastric resection, was performed in 1899 by Keetley and advocated by von Haberer in 1919. Judin and other Europeans and more recently some American surgeons have used this method with success and safety [1,9,11,12,15,16,23,27, 33,36,37,40,46–48,53,54,57,64,74]. The third method, nonoperative management, was successfully used by Redwood in 1870, later by Mullen and Wangensteen, and more recently by many other surgeons, with benefit [4,40,55, 61,68,69,73]. Recent reports show comparable mortality rates after use of each of these three methods of treatment. There are potential advantages of each method, application of which should be considered for individual cases [47].

The mortality rate with the acute episode of perforation is still too high in certain circumstances. With gastric ulcer, the rate is two to seven times that for duodenal ulcer even if it is benign [1,12,13,30,35,47,48,56,59,68]. In our series the rate for gastric ulcer was 30 per cent more than for duodenal ulcer. In addition, 4 per cent or more gastric perforations will prove to be malignant [1,47,68]. When the perforated ulcer has associated bleeding, the mortality is increased; 37.5 per cent of our patients with bleeding died [2,34,49,51]. Multiple ulceration is often present and probably contributes to the mortality [23]. With these circumstances gastric resection or vagotomy with ancillary procedure may give better results. With increasing age of the patient the death rate is higher, influenced by associated cardiac and other diseases, by higher incidence of gastric ulcer and also by longer delay of the older group in seeking treatment [8,12,17–19,31,38,40,43,47,57]. In several reports, the chronicity of the ulcer process was a definite factor in increasing the initial mortality [20,38,45,47,65,67–69].

In treating a patient with a perforated ulcer, one must consider not only the risks of the initial episode but also the mortality and morbidity associated with the future ulcer diathesis. Consideration must be given to the risk of dying in the future from the ulcer. This risk varies from 1 to 10 per cent and in our series was 2.8 per cent [3,10,13,14,18,20,21,24–26,29,32,41,58].

Patients with gastric ulcers have been reported to have a worse prognosis than those with duodenal ulcers [20]. In our series this was confirmed.

For a patient with an acute ulcer and a short, uncomplicated antecedent history, the outlook after recovery from the perforation is moderately good and is similar to that of a person having an ulcer with mild or moderate symptoms. In general, 75 to 90 per cent have been reported to be well or satisfactory [5,10,20,32, 44,45,47,52,66–69,71].

In contrast, the chronic patients with more severe processes will have more serious sequelae. This chronic group comprises 60 to 75 per cent of all those with perforated ulcers (77 per cent in our series). There have been reported a 1 to 9 per cent incidence of reperforation (6.7 per cent in our group), a 10 to 20 per cent or greater chance of hemorrhage (12 per cent in our series), moderate or severe symptoms in 20 to 35 per cent (51 per cent in our patients) and some risk

of obstruction dependent on the prior cicatricial process and often made worse by surgical closure of the perforation [*1,7,12,20,22,25,30,39,40–42,44,45,47,52,53,61,65,70,71,74*]. Because of the serious complications, performance of ulcer-curative surgery is indicated in most of this group. When performed as an elective procedure, it carries a mortality rate of about 1 to 5 per cent (1.7 per cent in our series). This rate is similar to that for gastric surgery without a history of perforation, and also is comparable to that in some small series of resections performed at the time of perforation.

Table v presents a comparison of the acute and chronic groups with data compiled from the literature and with our results noted in parentheses. Our patients did not show the correlation of increased initial mortality with chronicity as reported by some authors. The percentages of postoperative symptoms and of secondary surgery in our acute group were higher than usually reported. It has been noted that people having an occupation involving great stress carry a risk equal to that in patients with a chronic ulcer process [*47*]. Norberg has reported that of the 20 to 30 per cent of the patients who remain symptom-free, one-seventh to one-fourth are harboring ulcers.

In summary, patients with gastric ulcers might be treated best by excision and closure, or resection when feasible because of the risks of mortality, malignancy and future morbidity. Patients with associated bleeding might well be considered for ulcer-curative surgery in view of their high initial mortality after simple closure. For the acute duodenal ulcer patients who have had few or mild previous ulcer manifestations, simple closure is effective, or a nonoperative regimen can give good results as shown by many authors. Certainly, a major gastric procedure seems contraindicated at the time of perforation. If the acute ulcer patients remain asymptomatic for a year after perforation, they probably will stay well. The majority of patients with perforation who belong to the chronic group should have the selection of their initial management weighed very carefully, because this group has a higher initial mortality rate and too much subsequent disability and also there is a definite risk of dying from recurrent ulceration [*44,46,48,62*]. For these patients, ulcer-curative surgery should be contemplated either at the time of perforation or as an elective procedure later. The treatment of a patient with acute perforation should not be stereotyped but selective with consideration of factors influencing not only the immediate mortality, but also the manifestations of future ulcer disease.

TABLE V
ACUTE AND CHRONIC ULCER COMPARISON

Collected and Personal Data	Acute (%)	Chronic (%)
All cases	(22.9)	(77.1)
Duodenal	(22.5)	(77.5)
Gastric	(25.6)	(74.4)
Initial mortality	0–2.5 (13.0)	6–15 (8.0)
Postoperative symptoms	8.0–45.0 (60.0)	45–100 (77.0)
Second surgery	0–18.0 (28.0)	38–85 (50.0)

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DISCUSSION

CARLETON MATHEWSON JR. (San Francisco, Calif.): A statistical study such as this is a most important contribution particularly since it has been undertaken in an institution where reasonably accurate, long time follow-up care is carried out. Peptic disease is a malady which usually spans a great many years of one's life and complications may develop at any time, early or late, in the disease. It is therefore important that authentic follow-up studies extend over a period of many years. This study which encompasses, in part at least, a span of sixteen years is impressive and no doubt will be more so as more time is added to those cases operated late in the series. The figures reported this morning again emphasize the observation that the perforation of a peptic ulcer is an ominous sign in the course of peptic disease. It alters the immediate and ultimate prognosis so definitely that choice of treatment of the perforation becomes difficult.

An acute perforation of a peptic ulcer can be managed in a number of ways, the most popular being: (1) conservative medical management with continuous gastric suction; (2) simple surgical closure; (3) subtotal gastric resection; (4) excision, pyloroplasty and vagotomy. Each of these methods has its staunch advocates who have reported excellent results with the exclusive use of one or another.

There have been convincing series of cases reported which would indicate that it is safe for a capable surgeon to undertake definitive surgery such as gastric resection or vagotomy and pyloroplasty at the time of an acute perforation, but I know of no statistics that would prove that the morbidity from these procedures undertaken at the time of an acute perforation is any less than when the operation is performed as an elective procedure. This, I believe, is the crux of the matter. In this report over one half of the patients treated by simple closure subsequently died of their ulcer, required further surgery or continued to have moderate pain with hemorrhages or severe pain. Whereas it may be assumed that this group might have avoided these complications had definitive surgery been undertaken at the time of the perforation, what of the other one-half? Should they, too, have been subjected to definitive surgery and hence to the not inconsequential morbidity that goes with it? How could the group with poor follow-up records have been separated from the others? Dr. Hastings suggests that definitive surgery at the time of perforation should be considered in gastric perforation and in the duodenal perforation belonging to the chronic group to obviate the high incidence of ultimate morbidity and mortality in this latter group.

It has been our feeling that there is more than one way to manage this problem and for this reason we are reluctant to adhere too rigidly to one form of treatment. Occasionally, but infrequently, we choose conservative therapy, particularly if it appears that the peritonitis is localized and is remaining so. Usually a laparotomy is undertaken and if it seems evident that the condition has advanced to the stage that ultimately requires definitive surgery, we do not hesitate to undertake gastrectomy or whatever definitive procedure seems indicated as the initial procedure rather than simple closure. Usually we choose a simple closure. These patients are kept on a strict medical regimen and are requested to return eight weeks following simple closure for further study. If they are symptomatic in spite of medical management or have x-ray evidence of an active ulcer, they are advised to have more definitive surgical management. We have been impressed with the benign postoperative course encountered in that group of patients subjected to secondary surgical procedures. It appears as though the initial perforation with peritoneal contamination acts as a vaccination against subsequent peritoneal reaction.

Unfortunately, the follow-up records from our hospital will not permit a comparison with this series reported by Dr. Hastings. Our experience, however, has been similar to his and we would certainly agree that simple closure is not the com-

plete answer to this problem. Definitive surgery is permissible in a selected group of patients but this method of management should be confined to that group who obviously have symptoms in an advanced stage and who are good surgical risks. It is not permissible to subject all patients with acute perforations to either the immediate or ultimate morbidity and mortality associated with major gastric surgery.

I would like to congratulate Dr. Hastings upon a careful analysis of this perplexing problem.

NEWLIN HASTINGS (Los Angeles, Calif.): A number of cases have been treated by an ulcer-curative procedure but their number is not of statistical significance. We expect to carry on this follow-up study and hope to have more statistical data in the future.

The Natural History and Results of Surgical Therapy for Carcinoma of the Stomach

AN ANALYSIS OF 250 CASES

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DURING the past several years there has been widespread interest in the use of antineoplastic drugs, often as an adjuvant to surgical removal of solid tumors. The urge to try something new is particularly compelling in cancers which yield consistently dismal results after conventional operative excision. One of these is carcinoma of the stomach. For two and one-half years we have been participating with other hospitals in a study of the value of adjuvant chemotherapy used along with gastric resection for gastric cancer [1]. This has stimulated us to review the results of treatment for cancer of the stomach at the Veterans Administration Center, Los Angeles, during the ten years preceding the initiation of the adjuvant chemotherapy study.

This review was designed to provide a picture of the natural history of carcinoma of the stomach as it occurs in this hospital and to delineate our experience with various forms of treatment. We were especially interested in comparing the results of subtotal gastrectomy with those of total gastrectomy for this cancer.

MATERIAL AND METHODS

The study included all patients with a discharge diagnosis of carcinoma of the stomach who were admitted to the Veterans Administration Center, Los Angeles between January 1, 1948 and June 30, 1958 and who had not had a previous surgical operation for this condition elsewhere. This included all patients diagnosed as having scirrhous cancer, papillary or polypoid cancer, mucinous cancer and adenomacarcinoma. It did not include squamous cell carcinoma, lymphosarcoma or leiomyosarcoma. There were 250 patients in all, 248 males and two females. The study was closed on August 31, 1960 and follow-up was complete to that date except for four patients who were lost to follow-up at between seven months and over five years.

The data for each patient were placed on marginal punch cards for convenience in analysis and correlation. The information of greatest interest is present in the tables and the salient points from each table are elaborated in the text.

RESULTS

Table I presents the distribution of age at the time of onset of symptoms. The mean age was 62.2 years and the range was twenty-eight to eighty-nine years.

Table II enumerates certain other diseases which accompanied cancer of the stomach. There were seventeen patients who had pernicious anemia at the time carcinoma of the stomach was discovered and twenty-two who had had other independent cancers at some time in their lives. These latter included some cases of basal and squamous cell carcinoma of the skin. Although twelve patients had unequivocal histories of past duodenal ulcer, no active duodenal ulcers were found in any of the 250 patients. Only two patients had gastric polyps separate from their cancers.

TABLE I
AGE AT ONSET OF SYMPTOMS OF CARCINOMA OF THE STOMACH

Age (yr.)	No. of Patients
Under 34	7
35–39	6
40–44	8
45–49	6
50–54	27
55–59	51
60–64	54
65–69	45
70–74	18
75 and over	28
Total	250

Nine patients had a long history of gastric ulcer. At surgery or autopsy only cancer was found in five patients and a carcinomatous ulcer was found in four. One of the latter had an additional benign prepyloric ulcer.

In Table III the tumors are classified into three gross anatomical types.

The tumors were classified as to anatomic site as shown in Table IV. The prepyloric region was defined as extending 5 cm. orad from the pyloric ring; the cardia as 5 cm. of stomach about the cardioesophageal junction; the antrum as extending from the prepyloric region to the incisura angularis on the lesser curvature and directly opposite the incisura on the greater curvature; and the body and fundus as including the remainder of the stomach. There was no evident relation between anatomic site and duration of symptoms. However, of the five asymptomatic tumors two were located in the cardia and three in the body and fundus of the stomach. There was also no relation between anatomic site and gross tumor type except that linitis plastica involved the stomach totally in twenty-two of forty-three cases.

TABLE III
GROSS TYPE OF TUMOR

Type	No.	Per cent
Polypoid	82	33
Ulcerative	119	48
Linitis plastica	43	17
Unknown	6	2
Total	250	100

TABLE II
ASSOCIATED DISEASES IN PATIENTS WITH GASTRIC CANCER

Disease	No.	Per cent
Pernicious anemia	17	6.8
Other carcinoma	22	8.8
Duodenal ulcer	12	4.8
Hiatus hernia	4	1.6
Gastric polyps	2	.8

Table V correlates the duration of symptoms prior to admission with the gross anatomic type of carcinoma. The type of tumor appears unrelated to the duration of symptoms. The five asymptomatic patients died of other causes and carcinoma of the stomach was discovered at autopsy. Seventeen cases of cancer of the stomach were not diagnosed correctly until autopsy. It is of interest that 162 of the patients had symptoms for six months or less but that seven had them for five years or more before admission.

Table VI lists the presenting symptoms in order of frequency and correlates them with the gross type of cancer. The most common symptoms of weight loss, abdominal pain and nausea occurred with similar frequency in all gross types of cancer. Vomiting occurred most often as a presenting symptom in patients with linitis plastica. Anemia, melena and hematemesis were far more likely in patients with polypoid or ulcerative cancer than in those with linitis plastica.

In Table VII physical findings are correlated with gross tumor type. A palpable epigastric mass was least common in the ulcerative type

TABLE IV
ANATOMIC SITE OF TUMOR

Location	No.	Per cent
Prepyloric	51	20
Antral	24	10
Cardiac	28	11
Body and fundus	105	42
Total involvement	39	16
Unknown	3	1
Total	250	100

TABLE V

GROSS TYPE OF CANCER CORRELATED WITH DURATION OF SYMPTOMS

Duration of Symptoms	Total		Polypoid		Ulcerative		Linitis Plastica		Type Unknown
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.
Under 3 months	102	41	33	40	49	41	20	46	...
3–6 months	60	24	26	32	22	18	10	23	2
7–12 months	44	18	13	16	23	19	7	16	1
1–2 years	26	10	3	4	17	14	4	9	2
3–4 years	6	2	1	1	3	3	1	2	1
5 years and over	7	3	4	5	3	3	...	...	...
Asymptomatic	5	2	2	2	2	2	1	2	...
Total	250	100	82	100	119	100	43	100	6

of cancer. An enlarged liver, rectal shelf and ascites were most frequent in linitis plastica. One-third of all the patients had no physical findings related to their cancer of the stomach.

Table VIII shows the numbers of the various diagnostic procedures which were performed and their success in establishing a positive diagnosis. In forty-three of 222 patients who were proved to have gastric cancer at operation or autopsy, x-ray examinations of the stomach did not result in a diagnosis of cancer. A frozen section examined during operation failed to give a diagnosis of gastric cancer in nine patients subsequently found to have it. Even permanent sections of the operative specimen led to an erroneous diagnosis in two patients who subsequently died of cancer of the stomach.

Gastroscopy was a helpful adjunct in diagnosing some cases of gastric cancer. Table IX shows that gastroscopic biopsy was not always positive even though cancer was seen by the gastroscopist, but that it was positive in some cases even if the cancer could not be visualized.

Table X shows the frequency of metastases to different sites as determined at operation or autopsy, whichever came first. The high

TABLE VI

PRESENTING SYMPTOMS CORRELATED WITH GROSS TYPE OF CANCER

Symptoms	Gross Type of Cancer								
	Total		Polypoid		Ulcerative		Linitis Plastica		Unknown
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.
Weight loss	171	68	58	71	75	63	33	75	5
Abdominal pain	169	67	52	63	83	70	31	70	1
Nausea	163	65	52	63	77	65	28	64	6
Vomiting	117	47	31	38	57	48	24	55	5
Melena	109	44	36	44	59	49	12	27	2
Blood loss anemia	62	25	16	20	40	34	6	14	...
Pyloric obstruction	47	19	12	15	20	17	15	34	...
Hematemesis	44	18	13	16	28	24	3	7	...
Asymptomatic	5	2	2	2	2	2	1	2	...
Total patients	250	...	82	...	119	...	43	...	6

TABLE VII
PHYSICAL FINDINGS CORRELATED WITH GROSS TUMOR TYPE

Physical Findings	Gross Type of Cancer								
	Total		Polypoid		Ulcerative		Linitis Plastica		Unknown
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.
Palpable epigastric mass	64	26	27	33	20	17	15	35	2
Enlarged liver	74	30	23	28	34	29	17	40	...
Ascites	15	6	2	2	6	5	5	12	2
Abdominal tenderness	105	42	35	43	47	40	21	49	2
Palpable lymph nodes	24	9	6	7	13	11	4	9	1
Rectal shelf	27	10	7	8	7	6	10	23	3
No physical findings	83	33	33	40	35	29	14	33	1
Total patients	250	...	82	...	119	...	43	...	6

incidence of metastasis is striking. The most common sites of metastasis were abdominal lymph nodes and liver, but spread to the lungs and peritoneal surfaces were also common.

Table XI gives the length of time from onset of symptoms to the last follow-up visit or death. Of the entire group of 250 patients 149 were known to be dead within one year after onset of symptoms. Twelve of the patients operated on were alive at one to over five years after their gastric resection. All of the non-operated patients were dead, but five of these lived one or more years after their symptoms began. Only four patients were lost to follow-up.

Table XII shows the types of surgical procedure which were performed and correlates these with the number of patients alive, dead, and lost to follow-up. It also gives the number of patients upon whom autopsies were performed.

In Table XIII we see the length of survival after operation as related to type of operation undertaken. If no operation was performed, this table gives the length of time from onset of symptoms to death. Survival time is not given for five unoperated patients since we could not accurately determine the time of onset of their symptoms. It is obvious that gastric cancer is a uniformly fatal disease if allowed to pursue its natural course. The apparent "cures" were only in the groups in which the cancer was resected

TABLE VIII
SUCCESS OF DIAGNOSTIC PROCEDURES

Procedure	No. of Patients	Positive Diagnosis	
		No.	Per cent
Upper gastrointestinal x-ray examination	222	179	81
Gastroscopy	81	53	65
Gastroscopy with biopsy	15	8	53
Frozen section	58	49	84
Permanent section	169	167	99

TABLE IX
CORRELATION OF VISUAL AND PATHOLOGIC DIAGNOSIS IN GASTROSCOPY AND BIOPSY

Means of Diagnosis	Total	Cancer Verified by Positive Biopsy	Cancer Not Found in Biopsy Specimen
Patients undergoing gastroscopy and biopsy	15	8	7
Cancer seen by gastroscopist	9	5	4
Cancer not seen by gastroscopist	6	3	3

TABLE X
SITES OF DISTANT METASTASIS

Site	No.	Per cent
Abdominal lymph nodes	172	69
Thoracic lymph nodes	19	8
Liver	100	40
Lungs	47	19
Peritoneum	42	17
Adrenals	30	12
Bone or bone marrow	23	9
Genitourinary tract	20	8
Vascular and lymphatic thrombi	11	4
Central nervous system	6	2
Abdominal wall	6	2
Heart and pericardium	4	2
Total patients with metastases	195	78
Total patients with generalized metastases	88	35

TABLE XI
TIME FROM ONSET OF SYMPTOMS TO LAST FOLLOW-UP OR DEATH

Time Interval	Operated				Not Operated	
	Total Operated	Dead	Alive	Lost to Follow-up	Total Not Operated	Dead
Under 3 months	22	22	...	...	23	23
3–6 months	25	25	...	...	16	16
7–12 months	52	51	...	1	12	12
1–3 years	34	33	1	...	3	3
4–5 years	34	27	5	2	7	7
Over 5 years	16	9	6	1	1	1
Total	183	167	12	4	67*	67

* In five patients from this group the duration of symptoms could not be determined, since the time of onset was indefinite.

TABLE XII
TYPES OF SURGICAL PROCEDURE CORRELATED WITH SURVIVAL AFTER OPERATION

First Therapeutic Operation	Total Patients	Living	Dead	Lost to Follow-up	Autopsies
None	67	...	67	...	59
Exploratory only	56	...	56	...	34
Gastroenterostomy only	20	...	19	1	13
Subtotal gastrectomy	59	5	52	2	29
Total gastrectomy	38	5	32	1	24
Esophagogastrectomy	10	2	8	...	6
Total	250	12	234	4	165

TABLE XIII
LENGTH OF SURVIVAL AFTER OPERATION CORRELATED WITH SURGICAL PROCEDURES

Operation	Total	Under 3 Mo.	3–6 Mo.	7–12 Mo.	1–3 Yr.	4–5 Yr.	Over 5 Yr.	Living	Survival Not Given
None	67	23	16	12	3	7	1	...	5
Exploratory only	56	39	10	4	3	...	...	...	...
Gastroenterostomy only	20	14	2	4	...	...	...	...	...
Subtotal resection	59	13	13	9	14(1)*	8(3)	2(1)	5	...
Total resection	38	13	4	5	7	2(1)	7(4)	5	...
Esophagogastrectomy	10	4	2		2	1(1)	1(1)	2	...
Total number resected	107	30	19	14	23	11	10	12	...
Per cent of total resected	100	28	18	13	22	10	9	11	...

* The numbers in parentheses are patients living and clinically free of cancer at the time of this study.

TABLE XIV
FREQUENCY OF POSTOPERATIVE COMPLICATIONS AS RELATED TO SURGICAL PROCEDURES

Data	Total	Exploratory Only	Gastro-enterostomy Only	Subtotal Gastrectomy	Total Gastrectomy	Esophago-gastrectomy
Number of patients	183	56	20	59	38	10
Number of patients with complications	66	11	4	26	22	3
Per cent of patients with complications	36	20	20	44	58	30
Reoperated for postoperative complications	19	1	...	8	10	...
Average number of complications per patient	.54	.27	.45	.56	.97	.40

and they amounted to 11 per cent of these patients undergoing resection and only 5 per cent of the entire unselected group of 250. Study of the resected tumors showed that among the twelve survivors six had only contiguous extension of the cancer from its area of origin while six had nodal metastases. It is very possible that some of these twelve may yet die of cancer in light of the long survival after gastric resection in occasional patients who ultimately die from their cancer. However, taking the results as they stand, the difference of five survivors of fifty-nine for subtotal gastrectomy as compared with five of thirty-eight for total gastrectomy is not significant at the $P = .05$ level (P stands for probability).

Table XIV gives the frequency of postoperative complications associated with various surgical procedures, while Table XV tells the type of complication. The proportion of patients with complications was elevated in the total gastrectomy group as was the number of complications per patient. All of the four myocardial infarctions occurred in that group. Moreover Table XIII shows that the early mortality (within three months after operation) was 34 per cent after total gastrectomy as contrasted with the 22 per cent

TABLE XV
NUMBER OF POSTOPERATIVE COMPLICATIONS AS RELATED TO SURGICAL PROCEDURE

Complication	Operation					
	Total	Exploratory Only	Gastro-enterostomy Only	Subtotal Gastrectomy	Total Gastrectomy	Esophago-gastrectomy
Wound infection, dehiscence or hematoma	28	3	2	14	8	1
Pulmonary	22	4	4	6	5	3
Obstruction of anastomosis	10	1	...	6	3	...
Gastrointestinal fistula	5	1	1	...	3	...
Dumping syndrome	3	...	1	1	1	...
Ruptured duodenal stump	1	...	...	1	...	...
Ruptured line of anastomosis	3	...	1	...	2	...
Thrombophlebitis	3	1	...	...	2	...
Myocardial infarction	4	...	...	...	4	...
Other	19	5	...	5	9	...
Total number of complications	98	15	9	33	37	4

after subtotal gastrectomy. Although the data suggest that early mortality and numbers of patients having complications are higher after total than after subtotal gastrectomy, these differences are not statistically significant at the $P = .05$ level.

COMMENTS

The data contained in Tables I through XI are descriptive of the natural history of carcinoma of the stomach as it is seen in the hospital. Partially similar data are given by Marshall [2]. It is of interest that only 6.8 per cent of our patients had pernicious anemia at the time gastric cancer was diagnosed. The duration of symptoms gave no clue to the gross type of gastric cancer, except that linitis plastica tended to accompany symptoms of short duration while most cancers causing symptoms for over three years were of the polypoid or ulcerative type. The usual common symptoms of weight loss, abdominal pain and nausea were equally present in all three groups but pyloric obstruction was most characteristic of linitis plastica and bleeding from the cancer was most common with the ulcerative and polypoid lesions. One third of these patients had no positive physical findings associated with their gastric cancers. An enlarged liver, ascites or a rectal shelf were findings seen most frequently with linitis plastica.

An upper gastrointestinal x-ray examination was the most useful diagnostic procedure. Often several such studies were made on the same patient, resulting in a positive diagnosis in 81 per cent of patients with cancer. Frozen section at operation failed to yield a positive diagnosis in 15 per cent of patients who were later proved to have gastric cancer. A negative frozen section must be weighed with other evidence in deciding how to proceed during an operation. A gastroscopic biospy may prove of confirmatory value if the gastroscopist sees the lesion, but it may also establish the diagnosis when he cannot see the cancer and takes the biopsy from normal looking stomach.

The survival after onset of symptoms is almost always less than one year in the patient who has cancer of the stomach which is not resected, but a rare individual may live four or more years with cancer. The poor survival record for patients undergoing exploration only (Table XIII) undoubtedly reflects the advanced stage of the cancer which prompted the surgeon to do no more than that. Gastroenterostomy alone was of no palliative value.

Our special interest was centered on the results from surgical excision of the cancer. An excellent review of papers on end results of surgical treatment for carcinoma of the stomach is that by Lipp and Phillips [3]. They surveyed eighteen series of carcinoma of the stomach and found a median absolute five year survivorship (based on total number of cases with five year follow-up) of 7.1 per cent. They also found a median relative five year survivorship (of those resected) of 26 per cent, with the range among the eighteen series of 6.6 to 38.5 per cent. Although six of our twelve living patients have not yet been followed five years, the absolute survival rate is already 4.8 per cent, and the relative survivorship of patients after gastric resection is only 11.2 per cent. Thus our over-all results are in harmony with those previously published but tend to the low side.

Since 1944 one of us (W. P. L.) has been interested in finding whether total gastrectomy is superior to subtotal gastrectomy for carcinoma of the stomach. The early results of total gastrectomy at The Johns Hopkins Hospital appeared in 1947 and 1949 [4,5] and were encouraging. In 1960 Rush et al. [6] reported again on The Johns Hopkins Hospital experience, comparing eighty-two patients with gastric cancer who had total gastrectomy from 1940 through 1951 with 117 who had subtotal gastrectomy from 1940 through 1950. Their postoperative mortality was 12.8 per cent after total gastrectomy and 8.8 per cent after subtotal gastrectomy. This is in accord with our findings presented in Table XIII that thirteen of thirty-eight or 33 per cent of patients having total gastrectomy and thirteen of fifty-nine or 22 per cent of patients having subtotal gastrectomy survived three months or less, the ratio of the two groups being the same in the two series. It is evident that total gastrectomy carries with it a somewhat higher probability of complications and early mortality than subtotal gastrectomy.

Rush et al. also found a 9 per cent five year survival among sixty-nine patients with gastric adenocarcinoma treated by total gastrectomy as compared with a five year survival of 25 per cent among 117 patients undergoing subtotal gastrectomy for gastric cancer. Our survival figures given in Table XIII are not strictly comparable since our twelve living patients

have not all reached five years from operation, but survival figures based on these data must equal or exceed those for any later date. We have five survivors, all for four or more years, out of thirty-eight patients who had total gastrectomy for gastric cancer, or 13 per cent. This is slightly better than the results of The Johns Hopkins Hospital series. However, we have only five of fifty-nine or 8.5 per cent surviving after subtotal gastrectomy, which is in sharp contrast to their figure of 25 per cent.

Any decision as to the merits of subtotal versus total gastrectomy must hinge on the comparison between the results of these two procedures. Any valid comparison between these results requires that similar patients are allotted to the two treatment groups. Certainly we have no basis for speculation as to selection involved in the process of hospital admission. We know that in neither series were the admitted patients with resectable lesions randomly assigned to the two operative groups. Rush et al. presented evidence supporting the view that their findings held true even if the two operations were compared when applied only to cancers in the distal two thirds of the stomach. Certainly there is a possibility that total gastrectomy might be applied to more extensive lesions than subtotal gastrectomy. However, our low survival figures for subtotal gastrectomy could reflect a tendency to be willing to do a subtotal gastrectomy for palliation in the face of incurable spread, differences in patient material or differences in judgment as to what degree of tumor extension makes resection unwarranted.

Lawrence and McNeer [7] recently compared their results with subtotal and total gastrectomy for cancer of the stomach. Among patients who had subtotal gastrectomy there were 33 per cent five year survivals, while of those having extended total gastrectomy there were 17 per cent five year survivals. This again suggests that subtotal gastrectomy may be preferable to total unless there are special indications for the latter.

Rush et al. emphasized nutritional difficulties that may develop following total gastrectomy. In 1951 one of our total gastrectomy patients died sixteen months after resection of inanition and at autopsy no sign of recurrent cancer was found. This occasional problem might be helped by construction of a substitute gastric reservoir as recommended by Longmire and Beal [8].

A total of twelve patients in our series died of causes other than cancer, were autopsied and showed no signs of residual cancer. Beside the aforementioned patient with malnutrition, one patient died four and one half years after a subtotal gastrectomy of arteriosclerosis and nephritis and another died four years after esophagogastrectomy, of a cerebral accident. The remainder died shortly after operation of postoperative complications.

SUMMARY

A review of 250 patients with cancer of the stomach showed that only 4.8 per cent were alive on follow-up of at least two years. Five out of thirty-eight patients who had total gastrectomy, five out of fifty-nine who had subtotal gastrectomy, and two out of ten who had esophagogastrectomy survived to the close of the study. Although these findings tend to support the value of total gastrectomy for cancer of the stomach, other recent reports do not agree. Since even the best results from operation for cancer of the stomach are unsatisfactory, new forms of treatment are needed.

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DISCUSSION

ALLEN M. BOYDEN (Portland, Oregon): The thorough report of a recent experience with 250 cases of carcinoma of the stomach emphasizes again the disturbing fact that despite all of the advances in diagnostic methods and surgical technic and treatment, practically no improvement has occurred in the rate of survival and "cure" in this disease.

Diagnosis remains difficult in many patients. The symptoms are frequently mild and misleading, particularly in body and fundal lesions. Failures of x-ray diagnostic methods result in therapeutic delay in many patients. Gastroscopy has proved disappointing. In our experience it has added to delay more often than it has exposed the true diagnosis.

Yearly x-ray examinations of the stomach in all patients with achlorhydria and pernicious anemia as well as more frequent diagnostic exploration on suspicion are useful and at times rewarding. But these efforts at earlier detection cannot answer the over-all problem. The known natural history and biologic behavior of carcinoma of the stomach force the conclusion that we cannot expect real improvement in total end results so long as surgery remains the only modality available for hope of cure.

This conclusion, however, does not liberate the clinician from his responsibility to the patients who seek his help. Every effort at early detection must be undertaken, including insistence on repeated studies at short intervals when symptoms persist after original negative reports. Early exploration when gastric ulcer fails to heal or respond to careful medical management may yield real dividends. In many reports 20 to 40 per cent of the five year survivors will be patients with ulcers not known to be malignant before surgery or even until the final pathologic report discloses the true diagnosis. It is well known that in such cases the "cure" rate may approximate 50 per cent.

Dr. Clarke and his associates have focused particularly on the problem of total versus subtotal gastrectomy in the treatment of gastric cancer. I believe that their results, along with the results of others who have studied this problem, can lead to but one conclusion: the operation elected must be tailored to fit the particular lesion at hand and not be predicated on the basis of a preconceived standard total gastrectomy.

Because of the higher mortality for total gastrectomy, and particularly because of the severe crippling nutritional problems following total resection, I have never elected this operation unless forced by total or near total malignant involvement of the stomach. Resectable lesions of the cardia, fundus and upper body have been treated by esophagogastrectomy and esophagogastric anastomosis. Lesions of the lower third and midbody have been treated by subtotal resection. Frozen section of tissue from the line of resection will help to avoid inadequate resection. Wide resection of the duodenal cuff is of great importance.

Of much more importance than widening the amount of stomach removed is the willingness of the surgeon to perform a radical dissection of gastric ligaments, omenta and available zones of lymphatic spread. To be sure, the stomach does not lend itself to such dissection as easily as does the colon, rectum, or breast. However, unless one is ready to discard wide gland dissections entirely, the technic should be applied to gastric resections as well.

Unfortunately, it is still common to observe inadequate operations in which the surgeons expend little or no effort to remove accessible adjacent lymphatic zones. If tempered with judgment, reasonable extension of the operation in this direction will surely add to total survivors.

ARTHUR J. HUNNICUTT (Oakland, Calif.): Although the size or position of a malignancy in the stomach does affect the mortality, even more important is the type of malignancy.

One of our problems in interpreting statistics on carcinoma of the stomach is that all types are included. We should, statistically segregate cancers of the stomach into three categories: polypoid, ulcerating adenocarcinoma and scirrhus carcinoma or linitis plastica. Statistics which include all types of gastric malignancy are too pessimistic for polypoid lesions and too optimistic for linitis lesions.

A polypoid carcinoma may require minimal resection for high cure rate.

At the other extreme, the curability of linitis plastica is very depressing. Thus far in my total gastrectomies about half or seventeen have been for linitis lesions. The longest that any one of these has lived after total gastrectomy has been two years and six months. Our pathologist, Dr. Charles Baker, Merritt Hospital, Oakland, California, says he has never seen a linitis plastica cured.

At the present time I am completely pessimistic regarding curing these linitis cases. Therefore surgical removal appears to be only palliative and the decision to operate should be on this basis. I believe our choice in these cases is between doing a total gastrectomy or doing nothing. Even though the lesion appears to be small, the malignant cells infiltrate for great distances in the stomach wall and I believe that a subtotal gastrectomy is inadequate either for cure or palliation.

The outlook regarding ulcerating carcinomas is a better one. Unlike the linitis cases, a radical subtotal gastrectomy may be preferable if one can transect at a reasonable distance beyond the lesion.

I would like to ask the authors their opinion with regard to retroperitoneal lymph node dissection in

linitis plastica. I am of the impression from my small group that it does not gain anything and is not worth while. This does not apply to the ulcerating adenocarcinoma.

DAVID METHENY (Seattle, Wash.): I would like to express just one difference in point of view. We are all talking of how hopeless the prognosis is for this disease. Actually, we may have come a long way in the last twenty or twenty-five years. In 1939 I reported on 273 cancers of the stomach at the King County Hospital, which had occurred during the ten years before. Of these 273 cases, only seventy-one were submitted to surgery. Of these seventy-one, only twelve underwent a resection. Of these twelve, six died before they left the hospital. The six remaining of these original 273 left the hospital alive, with an attempt at being cured but all were dead within a year.

At the same time, in referring to the literature, I found that the University of Iowa had conducted a nine year study in which not a single patient had been operated on, and that at the Massachusetts General only one patient had survived for ten years.

Dr. Lundmark, my partner, and I have been associated now for a decade and a half. During the first decade we have had twenty-eight patients with malignancies of the stomach, a small series. Ten were operated on and closed; four had total gastrectomies; and one died, a death resulting from a leaking anastomosis after surgery. We have five patients surviving for over five years; one has survived fifteen years; and one died at the end of six years. However, we cannot quite count this last patient because he had a recurrence and his original disease was not carcinoma but sarcoma.

Then there is one other patient I would like to include in our series because I saw him just before I came down here. He has survived for four years and eight months and is apparently well.

So I think that we are making some progress with this disease. I hope the next twenty years will show as much progress as the last twenty.

WILLIAM P. LONGMIRE, JR. (closing): Some years ago attempts were made to improve the rate of cure of carcinoma of the stomach by applying more extensive operative procedures. This was not only true of cancer of the stomach but also of a great many other malignancies, and in the mid 1940's a number of people reported small series of cases in which total gastrectomy had been performed with fairly respectable mortality rates.

These results were not due to any marked improvement in surgical technical ability but primarily to various supportive aids in various types of surgical procedures.

Since that time many people have tried to analyze various series of cases in order to discover whether there is any definite advantage to performing total gastrectomy rather than subtotal gastrectomy. It is disappointing that in the fifteen to twenty years since total gastrectomy has been available with a respectable mortality rate, no one has been able to demonstrate any real advantage for this procedure. The present series more or less implies that total gastrectomy gives better results but this has to be accepted with reservations due to the small number of cases with which we were concerned.

We have gone through the stage of hoping that total gastrectomy would provide a partial answer for cancer of the stomach and at the present time we reserve this operation for use in highly selective cases. It is important to point out, however, that some of the distressing symptoms that have been associated with total gastrectomy are also encountered if one applies the very radical subtotal gastrectomy that has been described which leaves a pouch no longer than a man's thumb. When performing a radical subtotal resection, you can be prepared for many of the same symptoms that patients with total gastrectomies may have.

I, too, think that we cannot help but bear in mind what Dr. Metheny has pointed out; that is, that we do help some of these patients. Surgical excision is the only form of treatment available today whereby we can hope to help any of them. Until we have better methods, it is obvious that we should attempt to select an operation applicable to the individual case as best we can.

One can only conclude that in many cases gastric cancer, like many other malignancies, is a systemic disease which cannot be treated with a local procedure. Ultimately, we are going to have to depend on the development of some form of systemic therapy.

Acute Massive Hemorrhage from Gastroduodenal Ulceration

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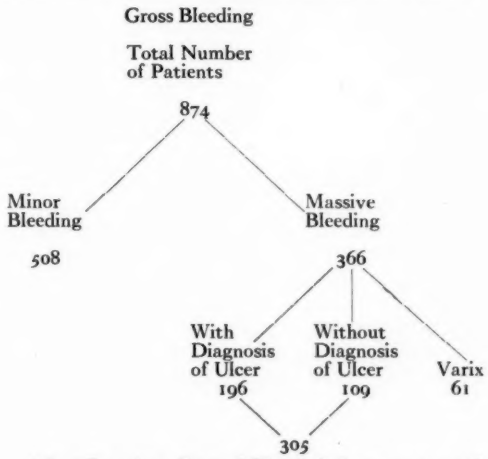
A FIVE year study of patients with upper gastrointestinal hemorrhage has been conducted on one of two serivces at the San Francisco General Hospital. The patients have been evaluated by the resident staffs of both the Medical and Surgical Departments and by one attending staff member from each department.

Uniform criteria applied to acuteness, severity and source of bleeding have been followed in evaluation and treatment. Acute hemorrhage means that the patient has had gross bleeding within five days prior to examination in our hospital. Actually, all but two patients who bled acutely and massively had evidence of active bleeding at the time of admission. Massive bleeding means that the hematocrit value has been lowered to thirty or less, representing an approximate loss of at least 40 per cent of the circulating red cell mass. These definitions of acute and massive are patterned after those suggested by Stewart et al.* The diagnosis of gastroduodenal ulcer has been based on a clear-cut history of ulcer or emergency roentgenogram of the upper gastrointestinal tract or both.

Eight hundred seventy-four patients were admitted for gross upper gastrointestinal hemorrhage. (Table I.) Three hundred sixty-six of these qualified as patients with acute massive bleeding. Since we primarily wished to evaluate the results in gastroduodenal ulceration with hemorrhage, we have excluded from this discussion the patients with hemorrhage due to varices. In this report, 305 consecutive patients with and without a diagnosis of ulcer bled acutely and massively. The average age of these patients was sixty-five.

Our purpose is to present a plan of management of patients with acute massive hemorrhage and discuss how this plan might influence two controversial issues: the indications for immediate operation and the dilemma of unexplained bleeding at the operating table.

TABLE I
BLEEDING FROM THE UPPER GASTROINTESTINAL TRACT*



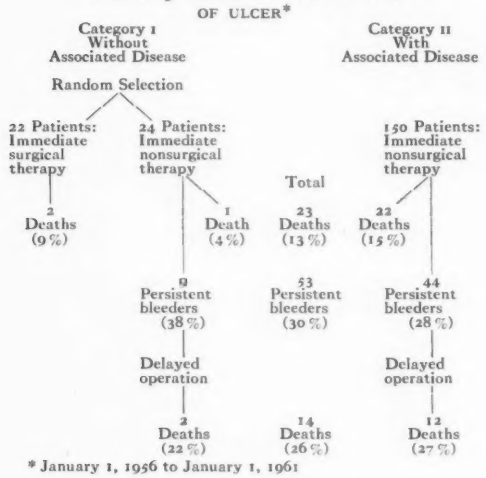
* San Francisco General Hospital January 1, 1956 to January 1, 1961.

PLAN OF MANAGEMENT

One hundred ninety-six patients were judged to have acute massive hemorrhage from gastroduodenal ulceration; the diagnosis was based on reliable history of ulcer or emergency roentgenogram of upper gastrointestinal tract or both. These patients were managed in the following fashion: Forty-six patients with bleed-

* STEWART, J. D., MASSOVER, A. J. and POTTER, W. H. Massive hemorrhage from gastroduodenal ulcer. *Surgery*, 24: 239, 1948.

TABLE II
ACUTE MASSIVELY BLEEDING GASTRODUODENAL ULCER. 196 PATIENTS WITH DIAGNOSIS OF ULCER*



* January 1, 1956 to January 1, 1961

ing ulcer had no critical associated disease and were placed in category I. A random selection of numbered cards decided whether initial treatment would be nonsurgical or surgical. One hundred fifty patients with severe hemorrhage had severe associated disease and were placed in category II. Initial treatment was nonsurgical. One hundred nine other patients who were bleeding acutely and massively did not have a diagnosis of ulcer confirmed by history or roentgenogram or both and were placed in category III. Initial treatment was nonsurgical. If the initial treatment was nonsurgical and active bleeding persisted, the patient was considered a candidate for delayed surgery when his hematocrit failed to rise above 30 per cent despite 9 units of blood. In categories I and II comparisons have been made between the results of immediate nonsurgical and surgical therapy and between immediate and delayed emergency operation. In category III the results of immediate nonsurgical therapy were analyzed.

CONTROVERSIAL ISSUES

Indications for Immediate Operation. From these comparisons the question is raised whether there is sufficient evidence to support the statement that the patient who bleeds acutely and massively from documented ulcer, warrants an immediate emergency operation. The following data seem pertinent. (Table II.) After immediate surgical therapy, the mortality in category I was 9 per cent. Following immediate nonsurgical therapy, the total mortality rate was 13 per cent in categories I and II. Seven out of ten deaths were due to hemorrhage rather than major associated disease. In this group of patients who were treated with immediate nonsurgical therapy, an additional 30 per cent persisted in bleeding and required surgical control after receiving 9 units of blood. The mortality rate in the group of fifty-three patients who persisted in bleeding and eventually had delayed emergency operation was 26 per cent. Seventy per cent of the patients had a history of chronic ulcer symptoms averaging ten years. In the majority of cases this, in addition to the complication of bleeding, was indication for elective gastrectomy. Approximately half of the patients who were operated upon had a proved gastric ulcer.

Although this evidence seems more real than apparent, it is premature to say that these data justify emergency operation on all patients bleeding acutely and massively from documented gastroduodenal ulcer. It is preferable to urge immediate emergency operation, at least in those ulcer patients who have no major associated disease and in whom there is a clear-cut indication for elective gastrectomy. For most other patients bleeding massively from ulcer, initial nonsurgical therapy may be the proper treatment. However, mortality figures need further critical analysis. The sobering influence of surgical mortality in these elderly, debilitated, welfare patients must be wisely interpreted in view of the significant number of nonsurgical deaths due to hemorrhage, the high incidence of persistent bleeding requiring a delayed emergency operation, the increased mortality rate associated with delayed operation, and the high incidence of chronic ulcer disease which warrants elective operation.

The decision regarding immediate operation is less of a problem when severe upper gastrointestinal hemorrhage occurs in a patient in whom there is no history of ulcer and in whom the x-ray examination is negative. Initial treatment in this group of patients should be nonsurgical and for these reasons: Exsanguination was rare. A number of these patients bled from sources other than gastroduodenal ulcer, such as: esophagitis, esophagogastritis associated with hiatus hernia, or gastritis associated with alcoholism. Most patients in this category

TABLE III

ACUTE MASSIVE HEMORRHAGE FROM UPPER GASTROINTESTINAL TRACT: X-RAY EXAMINATION FOLLOWED BY OPERATION OR AUTOPSY—SIXTY-NINE PATIENTS*

Findings	Per cent	
X-ray findings confirmed	67	84
Normal x-ray incorrect		
Superficial ulceration	17	
Substantial ulceration	10	
Positive x-ray incorrect	6	

* January 1, 1956 to January 1, 1961

TABLE IV

OPERATIVE FINDINGS IN EIGHTY-FIVE PATIENTS*

Findings	With Ulcer Diagnosis	Without Ulcer Diagnosis
Pathologic findings after initial exploration (70%)	52	7
Pathologic findings obvious after partial resection (27%)	12	11
No pathologic change (3%)	1?	2
Total	65	20

* January 1, 1956 to January 1, 1961

stopped bleeding. Only one in ten patients persisted in bleeding and after 9 units of blood required surgical control. When delayed emergency operation was finally necessary, the source of bleeding was usually gastroduodenal ulcer. In only two patients in category III was no explanation of bleeding found at the operating table.

The Dilemma of Unexplained Bleeding. The fear of finding no explanation for the bleeding at the operating table is an additional reason for the frequent procrastination in surgical management. This is a rare occurrence providing the surgeon elects to operate upon patients with severe hemorrhage who have a documented diagnosis of ulcer or who have no diagnosis of ulcer but persist in bleeding after receiving 9 units of blood.

The next point in this discussion concerns the accuracy of a diagnosis of gastroduodenal ulcer based on a reliable history of ulcer or x-ray findings or both.

Most of us agree that a history of ulcer in a bleeding patient is very helpful in establishing a diagnosis. Seventy per cent of our patients who were operated upon had a definite history of ulcer. Among these the sole error in diagnosis was questionable and concerned a probable marginal ulcer.

Not everyone agrees that emergency x-ray examination of the upper gastrointestinal tract is as reliable. Eighty per cent of these 307 patients had an emergency x-ray examination. Operation or autopsy followed x-ray examination in sixty-nine patients. (Table III.) The value of this study as an aid in diagnosis can be judged only by comparing the unbiased opinion of preoperative x-ray findings with the immediate operative or postmortem finding. The x-ray findings were confirmed in 67 per cent. The x-ray film was incorrectly interpreted as being normal in 27 per cent, but in 17 per cent the x-ray film failed to visualize superficial gastroduodenal ulcerations which was understandable after inspection of the pathologic findings. In 6 per cent, the x-ray film was interpreted incorrectly as being positive.

To sum up, the x-ray film showed what we thought it should in 84 per cent of the cases. Any errors were apt to be ones of omission. In patients operated upon with a preoperative diagnosis of gastroduodenal ulcer based on a history of ulcer or x-ray findings or both, no errors were made in diagnosis with the exception of one in the patient with a probable marginal ulcer.

It should be emphasized that at the operating table, unexplained bleeding was a common finding after initial examination. After resection had been performed, however, it was very uncommon even though the patient had no preoperative diagnosis of ulcer.

Eighty-five patients have been operated upon for acute, massive upper gastrointestinal bleeding—sixty-five patients had a preoperative diagnosis of ulcer and twenty did not. (Table IV.) The pathologic finding could be identified in 70 per cent of the patients after initial exploration. Ulceration was found in another 27 per cent after gastrotomy and resection. In only two and possibly three patients in this large group was no explanation for bleeding found.

The significant facts are these: One of four gastroduodenal ulcers was not identified after initial exploration. When preoperative diagnosis of ulcer was lacking, ulcer was usually not identified after initial exploration. Unexplained bleeding occurred rarely in this series of con-

secutive cases and in patients without a preoperative diagnosis of ulcer. Gastric resection following an initial negative exploration becomes less problematical in view of these figures.

When the bleeding site is not identified at the operating table, there are some who feel gastrotomy should be performed for the purpose of diagnosis which will then influence the decision whether or not to undertake a resection. In view of the high incidence of small, superficial ulceration, gastrotomy must constitute an accurate examination if gastric resection depends upon it. Is this the case?

Gastrotomy has been performed in twelve patients with unexplained bleeding after initial examination. On six occasions, this procedure disclosed small gastric ulcerations. In four other cases, the ulcer was missed but was found in the resected specimen. Gastrotomy failed to show four ulcers out of ten when ulceration was present. This is a high incidence of failure. Until there is more statistical proof of its value, gastrotomy might be performed in order to control bleeding or to allow removal of blood clots, but it probably should not be undertaken in order to come to a decision regarding gastric resection. It should be pointed out that if pathologic findings are not found in the resected specimen, the duodenum and the gastric remnant should be explored after resection and before completing the operation.

SUMMARY

Immediate emergency gastric resection is preferred treatment in patients with a diagnosis of gastroduodenal ulcer and acute massive hemorrhage who have no major associated disease and in whom there is a clear-cut indication for elective gastrectomy. For other patients with acute, massive upper gastrointestinal bleeding, initial nonsurgical therapy may be best.

The dilemma of unexplained bleeding is a rare occurrence providing the surgeon operates upon patients with severe hemorrhage who have a diagnosis of ulcer based on history or x-ray findings or both, or who have no diagnosis of ulcer but who persist in bleeding after receiving 9 units of blood.

DISCUSSION

VICTOR RICHARDS (San Francisco, Calif.): To my knowledge this is the third definitive study which has been made in an attempt to answer the problem of what is the best treatment for the person with massive bleeding ulcer.

The first approach to this problem was set in motion in 1948 when Dr. Stewart and his group in Buffalo decided that they would lay down certain rigid criteria for evaluation of patients with bleeding ulcer. One of the great difficulties in this field is that everyone who writes on the subject uses different criteria for judging what he is doing; I was therefore very pleased to see that Dr. Spicer has adhered rather rigidly to the Stewart criteria, which have become accepted in the evaluation of the bleeding ulcer. These criteria are: first, gross bleeding within a week; second, the patient should have lost at least 40 per cent of his total circulating blood volume; and third, the diagnosis of ulcer seems reasonably well established on a clinical basis.

Stewart decided to operate on all patients, and in his series of 124 cases he had fourteen deaths, which is approximately a 13 per cent mortality rate. His was the first controlled study which shows what might happen with routine operation on every massive bleeder, but it left open to question the virtue of judgment in the patient who is bleeding.

The second definitive study was made by Carlson and Dennis, again in New York, in which they tried to evaluate this intangible element that we call "judgment" in dealing with a patient. They decided that the best approach to this was the use of the statistical method of random selection of patients. They started off with Stewart's criteria, so that they followed pretty closely the same concepts of treatment, but they employed absolute random selection in deciding which patient would be treated by nonoperative treatment, which by immediate operation and which by the third method, defined as using "judgment." The concept of Dunphy and Hoerr was used to "judge" operative intervention.

The interesting thing is that, in their series, the results were the same in all three groups, regardless of the patients' age. They had a 14 per cent mortality rate in fifty-eight cases following nonoperative treatment; they had a 14 per cent mortality rate in thirty-nine patients in which they employed immediate operation. This, by the way, coincides well with Stewart's figures. And, they had a 14 per cent mortality rate when they used "judgment."

It was clear from Karlson's study that if you don't operate, a certain number of patients do bleed to death, and this was true even in those of the very young age group. If you do operate on patients after "judgment" or after random selection, the cause of death generally is not from massive hemorrhage but is from a complication of the surgical procedure.

Now we have Dr. Spicer's analysis, which is the third definitive study, and he has done something different. He has exercised judgment before beginning the analysis and, as you heard, he categorized his patients into those who had no associated disease and those who had associated disease which might make operation more likely to be indicated. It is again difficult to reach any definitive conclusion. It certainly seems clear that immediate operation carries the lowest mortality rate in any and all of these studies, or at least it is equal in treatment to anything that we do. Secondly, it seems clear that if a patient has had any previous indication for surgery at any time, the surgeon is probably better off operating before the patient reaches the stage of massive bleeding, since prophylactic gastric resection or prophylactic therapy certainly would seem well justified in the light of the results of these studies.

The third thing that was of interest to me was that Dr. Spicer had so few cases in which the diagnosis was no longer in doubt following the operative procedure. I suppose this fits in well with the rigid criteria that he used in selecting the cases. I think Dr. Cohn reported here a year ago on a group of elderly patients who were bleeding and who eventually bled to death, and in 30 per cent of them no cause for bleeding was ever found even at autopsy. I believe that the aged patient might be treated a little bit differently. It would seem that the best rule to follow for such patients would be to give them blood transfusions rather rapidly up to a reasonable blood volume. If they continue to bleed, or if they do not come out of shock, incident to proper transfusion, there should be immediate surgical intervention.

Unfortunately, all of this may be modified in the future as our concept as to what the proper treatment for ulcer really is and, of course, if those who perform vagotomies and merely tie off the bleeder come up with the answer that they have a lower mortality rate than that from any other procedure, even in acute bleeders, all of this may have to be modified. I certainly think that studies of this type are extremely important. We have to establish rigid criteria for what we are talking about; we have to use some sort of statistical approach in a large group of patients, and random selection seems almost essential.

For the majority of us who have to await the answer to this problem, it is best that we continue to exercise judgment. Careful consideration of these bleeding patients and the performance of an operation before he is "moribund" from excessive hemorrhage will enable us to save many of these massive bleeders.

Clayton G. Lyon (San Francisco, Calif.): Bill Spicer and John Carbone have put in a tremendous amount of time during the last five years, making their study. This probably is the third study, too, at this same institution. A number of years ago Dr. Goldman reviewed such cases, and then a little later Dr. Mathewson reviewed others on two comparable services, and these studies were more or less an evaluation of treatment and results. But when Dr. Spicer attempted this study, it was quite obvious it was difficult for a surgeon to know the diagnosis in those cases in which he operates purely on judgment. I think this is an earnest effort to categorize the cases so that we will have a little more exact information to go on when faced with patients with known duodenal ulcer.

Treatment of the Massively Bleeding Duodenal Ulcer by Ligation, Pyloroplasty and Vagotomy

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MASSIVE bleeding in chronic duodenal ulceration which is an immediate threat to the life of the patient remains a difficult and pressing surgical problem notwithstanding the substantial progress which has been made in recent years in the surgical management of peptic ulcer disease in general. The massively bleeding ulcer is responsible for more surgical fatalities than any of the other indications for duodenal ulcer surgery; yet it accounts for a relatively small per cent of all indications for surgical intervention, roughly 5 per cent according to our statistics.

The emergency calls for a procedure which will effectively arrest bleeding and prevent its recurrence. The operation should be one which can be performed with a minimum of time and trauma in this critical situation in which the patient is poorly prepared to withstand the stress of a prolonged, traumatizing procedure.

Because of the high surgical mortality associated with partial gastric resection in this emergency, a combined procedure of transfixion ligation of the bleeding vessel, pyloroplasty and vagotomy performed in one stage was adopted in our clinic some years ago on the theory that this relatively simple procedure would effectively deal with the needs of the situation by arresting the hemorrhage—the prime consideration—and by providing for long term healing. Our first use of it was early in 1949, following a surgical fatality while attempting to control a massively bleeding duodenal ulcer by partial gastric resection. Since then, forty-seven operations of ligation with nonabsorbable suture, pyloroplasty and vagotomy have been performed with results which have shown the method to have definite advantages over procedures we had used previously. During the period in which these forty-seven operations were performed, there were eight other operations in which variations in technic were used while bringing the procedure to its present form. These will be discussed separately.*

The criteria for inclusion in the massive hemorrhage group were: (1) evidence of massive bleeding from a chronic duodenal ulcer at the time of operation; (2) blood depletion manifested by rapid pulse, low blood pressure, and other evidences of impending or actual hemorrhagic shock; (3) low hemoglobin reading and a low hematocrit reading during the episode of bleeding. With few exceptions, the hemoglobin readings were 10 gm. per cent or lower and the hematocrit readings were 30 per cent or lower. There were several cases in which the readings were slightly higher but the requirements for inclusion in the study were satisfied in all other respects; (4) multiple blood transfusions immediately prior to operation. It has been a policy to consider three transfusions within twelve hours or six transfusions within one episode of bleeding as an indication for immediate surgical treatment. There have been frequent exceptions to this policy owing to the fact that some patients had received a number of transfusions prior to coming to our attention, and others had unrelated disease which contraindicated immediate operation and justified the use of a greater number of transfusions prior to operation.

A majority of the patients in the study were in the older age group. (Tables I and II.) Twelve

* Twenty-four of the cases in the present study were included in a previous report from our clinic [2].

TABLE 1

ANALYSIS OF CASES WITH STANDARD TECHNIC, 1949 TO 1960 INCLUSIVE

Patient	Age	Preoperative			Operation Length (hours)	Mortality and Complications	Postoperative Bleeding	
		Lowest Hemoglobin	Lowest Hematocrit	No. of Transfusions			Early (Two Weeks) and Late	Management
M. C.	61	5.8	18	7	3½			
R. R.	68	8	28	6	1½	Obstruction		
M. B.	40	5.3	20	8	3	Rebleeding	Early*	Surgical
H. H.	61	9.3	27	14	2½	Hepatitis		
J. S.	63	5.5	20	31	3½	Rebleeding	Early†	Medical
S. E.	49	11.2	24	4	2½			
E. L.	28	6.2	18	8	2½		Late	Surgical
R. C.	33	9.9	33	10	3			
L. S.	60	5.4	17.5	6	2			
H. W.	41	8.8	27	5	2½	Thrombophlebitis		
F. K.	50	11.4	25.5	8	2½			
H. W.	68	7.8	24	10	2½			
M. M.	65	8.5	26	7	1½			
D. B.	54	8.6	27	5	1½			
H. M.	52	8.2	26	13	1			
A. M.	69	5.2	17	6	2	Atelectasis		
M. H.	41	8.0	22	7	2			
T. L.	53	9.8	24	6	3½			
J. J.	50	9.9	27	18	3		Late	Surgical
R. I.	57	7.6	23	18				
W. G.	25	8.9	25	6	2			
W. F.	64	6.6	23	8	2½			
T. C.	66	6.8	22	5	2	Atelectasis		
J. W.	73	7.9	31	3½	1½			
L. V.	65	6.2	20	18	2	Wound dehiscence		
P. G.	75	7.5	20	6	2½			
H. D.	45	9.3	25	8	2			
A. S.	37	6.6	20	5	3	Pulmonary emboli		
H. W.	45	8.0	23	6	1½			
J. G.	30	6.7	24	9	2			
A. S.	46	8.0	25	10	2½			
D. O.	39	4.9	16	9	2½			
J. R.	37	9.3	23	5	3			
H. M.	63	4.3	15	9	3	Wound infection		
J. J.	26	7.8	26	7	4½	Atelectasis		
A. S.	61	8.3	25	7	1½	Atelectasis		
E. J.	59	7.4	24	5	2			
A. D.	64	9.3	25	6	1½	Pneumonia (death 6th day)		
W. P.	36	8.2	27	3	2			
A. M.	62	7.0	23	10	2			
J. H.	39	8.9	30	7	2½	Wound dehiscence		
G. H.	62	8.6	24	6	2			
F. M.	56	5.0	18	10½	1½	Rebleeding	Late	
J. D.	64	10.6	28	3	2½			
H. N.	31	7.8	25	7	2½		Late	Medical
B. H.	58	6.6	21.5	4	2			
V. L.	34	8.0	22	6	3	Wound infection	Late	Medical

* Six transfusions given.

† Twenty-two transfusions.

TABLE II

ANALYSIS OF CASES WITH DEPARTURES FROM STANDARD TECHNIC, 1949 TO 1960 INCLUSIVE

Patient	Age	Preoperative			Operation and Time (hours)	Mortality and Complications	Postoperative Bleeding	
		Lowest Hemoglobin	Lowest Hematocrit	No. of Transfusions			Early (Two Weeks) and Late	Management
R. L.	53	8.2	24	13	Gut ligation,* 1½			
C. H.	68	8	27	5	Gut ligation, 2½	Rebled (death 9th day)	Early†	Medical
A. S.	34	7.8	26	5	Gut ligation, 3			
J. B.	43	8.1	22.5	6	Gut ligation, 2½			
G. G.	44	7.7	23	6	Gut ligation, 2			
H. B.	57	7.5	23	9	Gut ligation, 3			
W. B.	60	10.2	31	4	Muscle overlay, 1½	Rebled (2 episodes)	Early‡	Surgical
S. M.	61	7.1	23	2	Muscle overlay, 5	Pulmonary embolism		

* Chromicized gut used in gut ligations.
† Four transfusions required.
‡ Twenty-nine and twelve transfusions required, respectively.

gave a history of severe alcoholism. Those suffering frrom chronic alcoholism were, in general, more difficult to manage than were other patients in the study. Several in this category showed hepatic changes characteristic of portal cirrhosis, with one having had a portacaval shunt five years previously. Other associated ailments were heart disease with recent or old infarction, eight cases; severe hypertension, six cases; and diabetes, one case. The associated diseases appeared to be of about the same incidence and seriousness as would occur in any large series of cases of massive bleeding in chronic duodenal ulceration. Seventeen of the patients had evidence of arteriosclerosis with a history of moderate to severe hypertension.

Chronic duodenal ulcer disease was known to have existed for two years or longer in the majority of the patients. There was well established evidence of chronic duodenal ulceration at the time of operation in all of the cases. The immediate preoperative diagnosis was made in most cases on the basis of previously diagnosed duodenal ulceration or by radiologic examination with contrast medium during the bleeding episode. In several instances, the preoperative diagnosis was assumed on the basis of vomiting of blood and passing of blood from the bowel.

OPERATIVE TECHNIC

Blood transfusions are started in two veins when the patient arrives in the operating room. Endotracheal anesthesia is used with gauze packing in the mouth around the tube to prevent aspiration of vomited blood. The abdomen is opened through a high transverse incision which extends beyond the rectus muscle on each side. After confirmation of the diagnosis, the pyloroduodenal canal is opened for exposure of the bleeding site. (Fig. 1.) The incision may be made somewhat longer than the usual 6 cm. in order to provide adequate room for ligation of the bleeding vessel. Clotted blood is evacuated from the stomach and duodenum, and the bleeding ulcer is exposed by retracting the edges of the gastroduodenal incision with several fine tooth Allis forceps. If bleeding is found to be temporarily arrested by a fresh clot, the clot is removed to activate forceful bleeding and thus clearly define its site. Mobilization of the duodenum is not only unnecessary but should be avoided, as it may cause tears in the inflamed duodenum and also may contribute to the formation of obstructing adhesions.

The transfixion ligation is made with a heavy, half circle, tapered needle (No. 4 Mayo) threaded with No. 30 cotton suture material. (Fig. 1.) The type of needle and the type of suture material are of special importance. The needle must be of a proper size and curvature to permit its easy manipulation within the small working space and must be heavy enough to withstand breakage as it is passed through

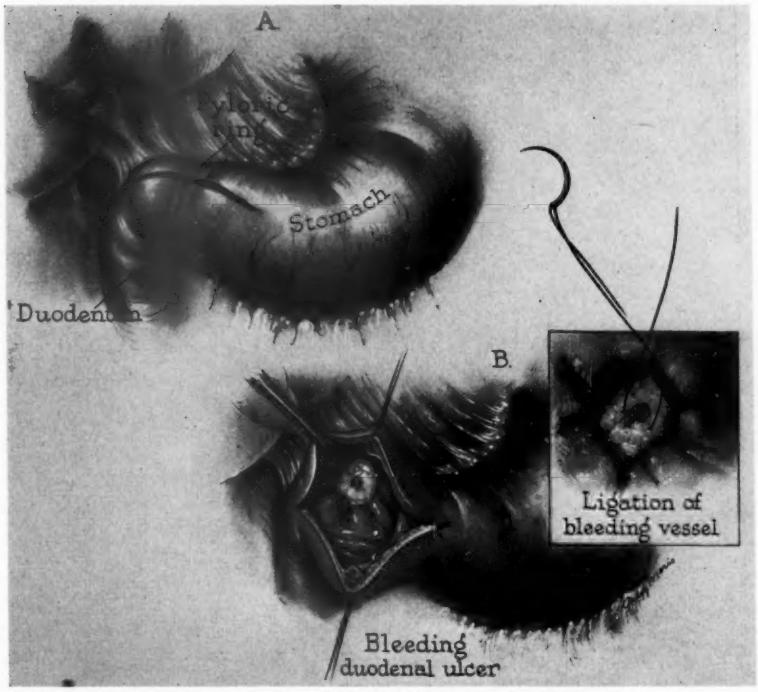

FIG. 1. Ligation of the bleeding vessel. A, longitudinal incision through anterior wall of pyloroduodenal canal to expose bleeding ulcer. The incision constitutes the first step of the pyloroplasty which is completed after arrest of hemorrhage. B, bleeding vessel exposed in calloused ulcer bed. Insert shows ligation of vessel with No. 3–0 cotton suture on stout, half circle, tapered needle.

the indurated ulcer bed. The suture material should be heavy enough to resist breakage as it is firmly tied around the bleeding vessel, and should be of nonabsorbable material which will resist the lytic effects of the digestive juices. The needle is passed deeply into the pancreas or other tissue which may form the floor of the ulcer. A common error is to insert the needle superficially because of fear of injuring neighboring structures, with the result that the bleeding vessel is not completely encompassed by the suture. While the danger of ligation of the common duct should always be kept in mind, there have been no instances in our series in which this has occurred. A study of the anatomic relationships in this area makes it apparent that the danger of obstructing the common bile duct is not great enough to offset the advantages of deep ligation. The suture is inserted in an over and over fashion to form a figure of eight as it is tied. (Fig. 1.) If bleeding persists, a second or even a third suture may be placed. Once the bleeding is arrested, the blood pressure and pulse rate tend to improve, and the operation may proceed more deliberately from this point. Before closing the pyloroplasty wound, the ulcer is observed for several minutes to make sure that the ligation of the eroded vessel is adequate. If the gastroduodenal and right gastroepiploic arteries are easily accessible, each is ligated in continuity as a further precaution against recurrence of bleeding. This additional procedure should not be attempted if edema and scarring make exposure of the vessels difficult.

The pyloroplasty is completed by closing the pyloroduodenal incision in a transverse direction. (Fig. 2.) The closure is made with a single row of interrupted No. 50 cotton sutures placed approximately 3 ml. apart. Single row closure with interrupted sutures is essential for the avoidance of infolding of tissues which would

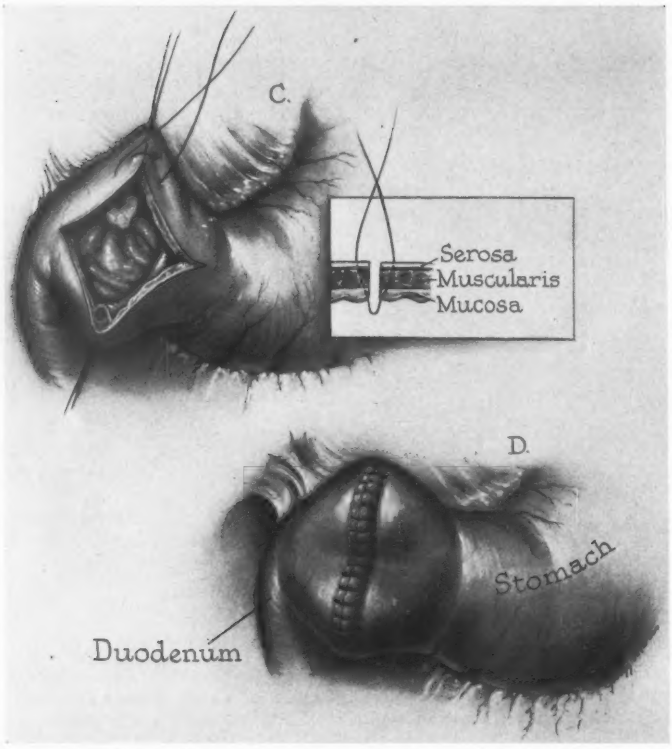

FIG. 2. Completion of pyloroplasty. The pyloroduodenal incision is closed in the transverse direction to complete the pyloroplasty. The closure is made with a single row of interrupted No. 5–0 cotton sutures, with accurate approximation of layers to prevent eversion of mucosa.

defeat the purpose of the pyloroplasty. The sutures pass through all layers in such a manner that mucosa is approximated to mucosa, muscularis to muscularis and serosa to serosa without protrusion of mucosa. This detail is important for the avoidance of adhesions which might distort the pyloroduodenal segment and cause postoperative obstruction. Neighboring omental tissue is tacked over the line of suture as an additional precaution against distorting adhesions. While there may be uncertainty about the patency of the lumen because of distortion by a scarred and edematous ulcer, this is of secondary importance, the main concern being the arrest of hemorrhage. If the pyloroplasty should prove to be inadequate, the difficulty may be corrected some days later by gastrojejunostomy or partial gastric resection.

The vagotomy is performed according to the Dragstedt principle in which the division of the nerves is made well above the level of the diaphragm. While the vagotomy would ordinarily be performed before the pyloroplasty to avoid contamination of the mediastinum by escaped gastroduodenal content, the advantage of ligation of the bleeding vessel as the initial step outweighs the theoretical danger of contamination. There has been no clinical evidence of mediastinal infection in any of our cases to date. The vagus nerves are exposed in the lower mediastinal area by making an incision through the membrane which covers the esophageal hiatus and retracting the esophagus together with the vagus nerves into the abdomen. Exposure for this maneuver is aided by the use of a specially designed retractor which elevates the liver anteriorly and cephalad away from the hiatus. The nerves are divided at a level between 4 and 6 cm. proximal to the junction of the esophagus and stomach. Division of the

nerves beyond this zone is less likely to include all of the components which supply the stomach because of divergent branching as the nerves approach the stomach. This is especially so with the right nerve.

After completion of the vagotomy, a gastrostomy tube is placed with its exit through the abdominal wall according to the method of Harris and Smith to provide gastric drainage during the first several postoperative days [1]. Oral feeding is withheld for five days following the operation, during which time appropriate fluids are administered intravenously.

It is advisable to complete the operation in one stage rather than perform the vagotomy some days later. If the vagotomy is postponed for a later stage, there is likelihood of rebleeding before the vagotomy is accomplished.

RESULTS

There has been one surgical death in the group of forty-seven patients in which the prescribed technic was adhered to. This death was in a patient, age sixty-four, who had suffered a cerebral vascular accident two weeks before his operation. He died on the sixth postoperative day with death attributed to bronchopneumonia. There was no autopsy.

Two patients in the group had episodes of rebleeding within a week following operation. One was treated by hemigastrectomy, and the other was treated medically. Both recovered satisfactorily without recurrence of bleeding. There was late recurrence of bleeding in five patients, the bleeding occurring eleven months to five years after operation. Two of the recurrences were treated by medical means, two by hemigastrectomy and one by subtotal gastrectomy of the Billroth II type. The patient with the secondary operation of subtotal gastrectomy, which was performed four and one half years after the original operation, had fatal rebleeding from the site of anastomosis seventeen days after the resection. Of the other patients with late rebleeding, all remain well without further evidence of bleeding at the time of the latest follow-up. All except one have been followed for four years or more, and the one exception has been followed for eighteen months.

One patient showed signs of partial obstruction postoperatively due to inadequacy of the pyloroplasty. The obstruction was overcome by a gastrojejunostomy performed twenty-five days later.

There were two cases of partial abdominal wound separation. Repair was successful in both.

There were no other serious complications in the group of forty-seven patients.

GROUP WITH VARIATIONS FROM THE STANDARD TECHNIC

During the same period in which the operations in this series were performed, there were eight operations for massive bleeding in which the procedure was on the same principle but differed in important technical details. (Table II.) In six the bleeding vessel was ligated with chromicized gut instead of cotton. There was fatal bleeding in one of these cases nine days after operation. It is possible that the rebleeding was the result of lysis of the ligature by the digestive juices.

Suturing of free muscle tissue over the site of bleeding was resorted to in two cases. There was rebleeding in one. There does not appear to be any particular advantage in the use of this maneuver, and there may be an actual interference with precise ligation.

COMMENTS

In applying the combined operation of ligation with nonabsorbable suture, pyloroplasty with one row closure, and vagotomy of the Dragstedt type to arrest massive bleeding in the chronic duodenal ulcer, it is essential that exact details of the technic be adhered to. The ligation should be made with a heavy, half circle needle which will not break as it penetrates the calloused ulcer bed and with nonabsorbable suture material which will resist the lytic action of the digestive juices. The type of pyloroplasty is also of special importance. A simple pyloroplasty with one row closure has the twofold advantage of facilitating exposure and ligation of the bleeding vessel and of providing a satisfactory means of overcoming the delayed gastric emptying induced by vagotomy. The Dragstedt supradiaphragmatic vagotomy, which is the final step in the procedure, promotes early healing of the ulcer and protects against late recurrence.

The low surgical mortality and morbidity and the satisfactory long term results obtained with

the use of this combined procedure are arguments for its use in the critical situation of massive bleeding in which simplicity and time are prime considerations.

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DISCUSSION

Louis G. Brizzolara (Berkeley, Calif.): Dr. Weinberg's method of management of the massively bleeding duodenal ulcer has an extremely low mortality and morbidity rate and, I believe, is the treatment of choice in this difficult situation.

For the past four and one-half years I have been using Dr. Weinberg's method of pyloroplasty and vagotomy for the surgical management of all duodenal ulcers and have been extremely satisfied with the results.

I have had personal experience (at the San Francisco Veterans Administration Hospital and with private patients) with twenty patients that fit the criteria of Dr. Weinberg's massive hemorrhage group. All these were treated as outlined in today's discussion. There were no deaths in these twenty patients. Their ages varied from twenty-one to sixty-eight years; fourteen of the patients were over fifty years of age. Two of these patients required reoperation in the immediate postoperative period: one had a cardioesophageal ulcer that continued to bleed, in addition to the duodenal ulcer; the other had a high posterior gastric ulcer in addition to the duodenal ulcer; both of these gastric lesions were controlled by suture ligation. The patients made an uneventful recovery without further bleeding. One patient had recurrent bleeding on the seventh postoperative day, responded to multiple transfusions and has had no subsequent difficulty.

I have followed Dr. Weinberg's procedure in all respects except for the abdominal incision. In some patients with a narrow and long thorax and acute angulation of the ribs at the ensiform process, I have found that the midline upper abdominal incision through the linea alba seems to afford better exposure of the cardioesophageal area. This midline incision, however, makes it difficult to use Dr. Weinberg's special retractor.

Dr. Weinberg mentioned ligation of the gastroduodenal and right gastroepiploic arteries in addition to transfixing the vessel in the ulcer bed. This was not done in any of the twenty cases.

Dr. Weinberg emphasized the importance of proper needle and suture material to control the bleeding vessel. This bears re-emphasis, as it is the crux of the method of controlling the bleeding. The needle must be stout enough to penetrate deeply into the indurated ulcer bed without breaking. The suture material must be heavy enough so as not to break or cut through the tissues (No. 20 cotton is used).

I have been most pleased with the results of pyloroplasty and vagotomy management of the massively bleeding duodenal ulcer and believe that it is the treatment of choice at the present time.

Jack M. Farris (Los Angeles, Calif.): Appraisal of the poor results which have been achieved in the past in the treatment of bleeding duodenal ulcer usually indicated that operation had been postponed too long and that the so-called failure of medical treatment actually implied a regrettable deterioration in the condition of the patient. This program had been elected in the past because of the unwillingness of surgeon and internist alike to adopt an implement at hand, namely, a formidable gastrectomy, and this program was elected with a mistaken, expectant hope that the bleeding would cease. The mortality from the operation (gastrectomy) was 10 per cent if performed early and became 70 per cent if performed late.

With Dr. Weinberg's philosophy, this concept, I think, has now changed. Logically, the first effort to treat bleeding duodenal ulcer by surgical operation was to ligate the bleeding point, as Dr. Weinberg has pointed out. But unfortunately, an inability to simultaneously alter the fundamental ulcer diathesis, allowed juice of low pH and high hydrogen ion content to redigest the vessel with renewed bleeding. So these experiences then led to the adaptation of gastrectomy. Vagotomy and pyloroplasty now allow suture of the bleeder promptly, a philosophy consistent with the surgical arrest of hemorrhage elsewhere in the body.

A great deal has been said previously about the criteria of the gastric bleeder and we believe that with the new philosophy (the philosophy of Southern California) very few patients are going to exhibit hematocrits of 30 per cent; and very few patients will receive 9 units of blood because with this lesser maneuver available it will be possible to employ surgical treatment earlier, before deterioration to these levels has occurred.

If the history of ulcer is short or ill defined, we believe that the circulation should be brought to normotensive levels by an appropriate amount of blood, and if bleeding recurs operation should be carried out as outlined by Drs. Hoerr, Dunphy and Gray. But if the ulcer diathesis is well defined, we believe in transfusing to a satisfactory circulatory status followed by prompt operation (in the absence of recurrent bleeding). Therefore, we rarely allow a

patient to become a so-called "massive" bleeder by the old criterion. It would seem that a new criterion should be added: We propose that a patient who exhibits a systolic blood pressure of 80 mm. Hg has lost 40 per cent of his blood volume and should be included even though his hematocrit and hemoglobin levels have not fallen to the levels described by Stewart (hemoglobin 8 gm.).

Finally, I would like to say that if one analyzes what occurs to a patient when his doctor successfully combats an episode of bleeding, one realizes that he has really accomplished very little in the patient's life as a whole. Although he has stopped bleeding, he still has his ulcer and it is necessary for him to return to his ulcerogenic environment with the prospect of another episode of bleeding staring him in the face. We speak a great deal about mortality from bleeding ulcer but I think more emphasis should be placed upon the morbidity. The world is filled with people who have successfully avoided an operation but live an unhappy and dyspeptic life.

We also believe that pyloroplasty and vagotomy is the operation of choice for all duodenal ulcers. In 164 such patients we have had only four failures. Our experience with this operation started in 1952 as result of the stimulus provided by Dr. Weinberg. Approximately a third of these patients have been bleeders, and thirty-three of them have been so-called massive bleeders. We have had two deaths in the massive group. I am certain that we would not have operated upon either of these patients if we had believed that gastrectomy would be necessary because they were such desperate risks. We continue to use it, and, contrary to other new procedures in surgery, continued experience with this method has increased rather than decreased our enthusiasm for it.

CLARENCE J. BERNE (Los Angeles, Calif.): Evaluation of a surgical method for control of bleeding duodenal ulcer should include analysis of certain important factors when comparisons are made with other methods. These factors are: (1) the criteria used for placing cases in the category of massive bleeding; (2) the size and location of the ulcer; (3) the kind of hospital; (4) surgery performed by residents in training or by experienced surgeons; (5) severity of the indications for operative intervention; and (6) the age of the patient. The age is the most important of these considerations.

With each of several methods of treatment used at the Los Angeles County Hospital, mortality rate for massively bleeding ulcer is low in patients less than fifty years of age. The mortality rate begins to climb steeply in the group between sixty and seventy years. This is also true of perforated peptic ulcer and acute cholecystitis. Results in the seventh decade best reveal differences between competing methods of treatment if the other factors are relatively constant. Both Dr. Weinberg's fatalities occurred in this age group.

Like Dr. Weinberg, our own series of massively bleeding duodenal ulcer cases treated by pyloroplasty, suture ligation and vagotomy, has now covered a long period of time. We began using this method in 1950, and are gratified with the results. However, we treat very large duodenal ulcers by the Billroth II type operation. In this small group the ulcer is excised when technically feasible; otherwise the bleeding point is sutured and the ulcer treated by exclusion.

The Billroth II operation fundamentally is a gastrojejunal shunt. Such a shunt will almost invariably cure duodenal ulcer, whether performed as a simple gastroenterostomy or by the Billroth II method. In the latter, the distal gastrectomy is added only to acceptably reduce the incidence of gastrojejunal ulcer and is in no way a factor in the cure of duodenal ulcer.

Most of our massively bleeding duodenal ulcers are of lesser size and are treated by pyloroplasty, suture ligation and vagotomy. Following this procedure the ulcer heals very rapidly. The rapid healing prevents rebleeding, which is essential to success with any method in which the ulcer is not excised. The vagotomy eliminates tonic hypersecretion due to vagal overactivity. Additionally, it reduces responsiveness of the antrum and of the parietal cell mass to all postcibal phasic stimuli. The antrum therefore secretes less gastrin and there is decreased response to that which is secreted. Additionally, the pyloroplasty reduces intra-antral pressures and thereby decreases phasic antrogastrin stimulation. Anatomically the antrum remains, but physiologically its activity is greatly reduced.

Consideration of the foregoing will make clear the fact that the newer surgery for duodenal ulcer recognizes that gastrojejunal shunting will never lead us to a physiologic operation for the cure of duodenal ulcer. A physiologic operation must maintain gastroduodenal continuity and thereby directly titrate surgical alterations against the ulcerogenic mechanism. At present pyloroplasty and vagotomy provides the simplest operation of this type.

No competing, basically similar operation has yet been shown to better the effects of complete vagotomy. We know that there are technical pitfalls in consistently obtaining complete vagotomy. We must recognize that there may be a physiologically superior type of pyloroplasty awaiting discovery. There is no published proof that, in conjunction with pyloroplasty and vagotomy, suture ligation of the bleeding vessel adds to control of bleeding duodenal ulcer. However, we believe that it does.

Finally, many surgeons doubt the impregnability of shunting procedures but are not yet convinced that pyloroplasty and vagotomy is a superior

method. It is necessary that more evidence be submitted.

EDWARD N. SNYDER, JR. (Pasadena, Calif.): Dr. Anthony Steller, Dr. Berne and I are in the process of analyzing the results of surgery for massively bleeding peptic ulcers on the University of Southern California surgical services at the Los Angeles County Hospital. Included in this group are eighty-five patients who have undergone vagotomy, pyloroplasty and stick-tie of a bleeding vessel in a duodenal ulcer. Our analysis is incomplete, but I think we can justify a few comments and comparisons with Dr. Weinberg's paper.

There is a striking similarity between our cases and those of Dr. Weinberg concerning age distribution, chronicity of ulcer symptoms, hemoglobin determinations, presence of shock, indications for surgery, and time of operation. Even the incidence of rebleeding after surgery and reoperation are almost identical.

The mortality rate in our series was considerably higher than that reported by Dr. Weinberg; we had thirteen deaths, a mortality rate of about 15 per cent. All deaths occurred in patients fifty years of age or over and nine of the patients were over sixty years of age. This is a mortality rate of about 8 per cent in patients under sixty, and 25 per cent in patients over sixty. These data again emphasize the increased lethality of bleeding duodenal ulcer in patients sixty years of age and over.

I cannot be sure, but I think our study is going to reveal that in some cases we perhaps erred in delaying too long from the time of admission to operation. Of Dr. Weinberg's patients only 23 per cent had ten transfusions or more before surgery; whereas, 70 per cent of our patients had ten or more transfusions and almost all of these were given preoperatively in both groups of patients. I think Dr. Weinberg's results, as pointed out by Dr. Farris, speak very well for the more aggressive surgical attitude in the treatment of bleeding duodenal ulcer.

Since the inception of our policy of vagotomy, pyloroplasty and suture ligation in 1950, Dr. Berne has insisted upon ligation both above and below the hole or the clot in the gastroduodenal artery. The use of at least two suture ligatures, one above and one below the perforation, is routine.

Dr. Weinberg has stressed the importance of using nonabsorbable sutures for stick-ties. We question this. According to his own figures, eight patients rebled who had been treated thusly, and one of six patients rebled in whom catgut was used for the suture ligature. Now, according to my simple arithmetic, this means that about one of six rebled regardless of what sutures were used.

In our series, No. 0 or 1 catgut was used for ligation of the bleeding vessel in seventy-two patients, and nonabsorbable suture in thirteen. Rebleeding occurred in both groups; however, the rebleeding was not from the ligated vessel in any case in which reoperation or autopsy was performed. Therefore, I think the method of suturing and not the material is the important fact and this is also concurred in by Dr. Berne.

Dr. Weinberg's fine paper speaks well not only for him, but for the splendid training he gives his residents.

J. ENGLEBERT DUNPHY (Portland, Ore.): I would like to say a word about selection of cases, with particular reference to classification. A patient who has been bleeding for five days and has a hematocrit of 30 per cent or less is not a massive bleeder in our way of looking at it. He is a chronic oozer. If one opens the carotid artery survival for five days is impossible, and the exsanguinating bleeder—and we should use the term "exsanguinating hemorrhage"—is the one who will not respond to massive transfusion and requires operation for that reason.

I think it is the best and most practical criterion, and as Dr. Farris has pointed out, with a somewhat lesser operative procedure appearing to be valuable, this criterion becomes of even greater importance.

Another point about selection, which was touched upon by Dr. Berne, that is vitally important and which is not solved by the method of randomization, is the patient population. It does not make much sense to randomize treatment in a county hospital and then compare those figures with randomized treatment in a private clinic since they are not the same type of patient. When we were at the Peter Bent Brigham Hospital, our mortality rate from this disease fell progressively, so that it almost seemed, in relation to duodenal ulcer, that massive bleeding was not a problem. However, in encountering patients at the City Hospital in Boston, the factors of age and associated disease were immediately obvious. The patient over sixty-five with pulmonary insufficiency and with vascular disease and cardiac disease is the patient upon whom we are focusing, and randomized treatment in this particular group of patients might be of great value.

I want to stress one other point. I do not think any form of randomization should include a procedure which does not control hemorrhage. I object to the study of Drs. Carlson and Dennis because they did not operate on patients who were bleeding to death, as in their series a few young patients did bleed to death. This is a bit like randomizing the treatment of fractures by bending some at a 45° angle to see how well they may heal.

Finally, I believe that the contribution of Dr. Weinberg and Dr. Farris is a major advance. It will take some time for us to know exactly where this operation belongs. I suppose it will be in the treatment of the complicated bleeder, namely, the patient over sixty-five with associated disease, since

in healthy young patients the mortality for either gastric resection or pyloroplasty and vagotomy would seem to be very low.

For the past year we have been using vagotomy and pyloroplasty on the County Hospital Service at the University of Oregon, and are very favorably impressed with the results to date. The series is still small, but at the present writing the results are comparable to those that have been reported here today.

JOSEPH A. WEINBERG (closing): The remarks that have been made are an indication of high interest in a subject which offers many difficulties.

I am particularly pleased with Dr. Brizzolara's comments on his satisfactory experience with the procedure and would second his emphasis on important details in the technic.

I agree with Drs. Farris and Dunphy that the hematocrit level is not in itself a satisfactory means of determining which case should be included in a study on treatment of the massively bleeding ulcer. A low hematocrit in the absence of other evidence to indicate sudden massive blood loss would be much more likely associated with a chronic anemia which is quite another problem. This has been taken into consideration in the present report.

Dr. Berne has brought up the question of distinguishing between ulcers on the basis of size and location. I can only say that we have made no distinction on this basis in determining the type of treatment to be used. Some of the lesions in our group would be classified as "giant" ulcers. Dr. Berne's comment on adequacy of vagotomy is pertinent. One might expect more occurrences of incomplete vagotomy in this emergency than there would be in less urgent situations, and this may account for some of the cases of rebleeding.

Regarding Dr. Snyder's comment on the method of ligating the bleeding vessel, we have not used this method and I can make no comment on it from personal experience. The question of the relative advantages of absorbable and nonabsorbable suture in ligating the bleeding vessel remains open. I can only say that our experience with the nonabsorbable suture material has been so satisfactory that we would not like to discontinue its use.

Re-evaluation of Temporary Gastrostomy as a Substitute for Nasogastric Suction

GORDON KNIGHT SMITH, M.D. AND JACK MATTHEWS FARRIS, M.D., *Los Angeles, California*

WHEREAS intravenous electrolytes will prolong the lives of animals with pyloric obstruction, prevention of ingested atmospheric air is the only means of protecting animals against the lethal effects of intestinal obstruction at lower levels [*18*].

Decompression of the gastrointestinal tract in humans is also life saving in certain pathologic conditions (i.e., ileus and acute gastric dilatation etc.). In the past, exclusion of swallowed air has usually been implemented by some type of nasogastric tube. The numerous contributions of Westerman [*21*], Kanavel [*12*], Ward [*20*] and Wangensteen [*19*] have perfected this mode of surgical therapy.

Rarely, major complications may occur as a result of the presence of a nasogastric tube. Additionally, there is an almost universal aversion to the tube, long remembered as a most discomfiting experience associated with recovery from certain major operations. A detailed documentation of complications due to nasogastric suction has previously been reported [*4,11*].

MODE OF DECOMPRESSION

Because of poor tolerance for prolonged nasogastric suction, particularly in seriously ill patients, other procedures have been devised to provide decompression of the gastrointestinal tract.

In 1939 Horsley [*10*] suggested double catheter gastrostomy for decompression following subtotal gastrectomy. Allen and Donaldson [*1*] in 1942 suggested jejunostomy for decompression of the stomach postoperatively and in 1953 Gilchrist [*5*] described the use of a Levin tube passed through the pylorus during abdominal operation and brought out through a stab wound in the abdominal wall as temporary gastrostomy. Others have occasionally utilized similar or related procedures [*15*].

In 1954 we began using a Foley bag catheter when performing temporary gastrostomy and reported its use in seventy-two patients [*4*]. Since then further experience with this method has been achieved and, additionally, data have been collected on over 2,500 patients in whom temporary gastrostomy as a complementary procedure has been utilized.

The purpose of this report is to re-evaluate the indications for the technic and, more importantly, to analyze certain distressing complications.

SELECTED INDICATIONS FOR GASTROSTOMY

Decompression of the gastrointestinal tract following most operations upon the stomach or intestine is probably not necessary, although in certain selected instances it may be life saving.

For example, it is rarely necessary in the ordinary type of gastric resection and neither gastrostomy nor nasogastric suction is employed. Although in the past it was felt that some type of suction should be routinely utilized in the operation of vagotomy and pyloroplasty, at the present time, the possibilities of omitting this maneuver are being explored. A brief preliminary experience indicates that many patients may have a smooth convalescence after this operation without any type of decompression. When vagotomy and pyloroplasty are employed for a bleeding duodenal ulcer, decompression would seem important to prevent stasis and stimulation of the antrum, with an increase in gastric secretion sufficient to prevent healing of the ulcer bed.

Temporary gastrostomy has proved to be

particularly valuable in patients with pulmonary disease, particularly chronic bronchitis and emphysema so frequently associated in patients with duodenal ulcer. A nasogastric tube, likewise, is poorly tolerated in patients with cardiac decompensation, and in the young and aged. In addition, certain patients undergoing major operations, such as portacaval anastomosis or resection of aortic aneurysm, may require prolonged decompression of the gastrointestinal tract and temporary gastrostomy may well be a good choice in this instance. It is particularly valuable in patients with esophagitis, who are operated upon for repair of hiatus hernia combined with vagotomy and pyloroplasty. Other patients in whom prolonged decompression is indicated and who may well enjoy the comforts of temporary gastrostomy are those with intestinal obstruction, peritonitis, pancreatitis; those with abdominal trauma, particularly when combined with thoracic injuries; and those who have a conditioned repulsion to the tube as a result of previous exposure to the method.

FIG. 1A. Modified Hesseltine clamp.

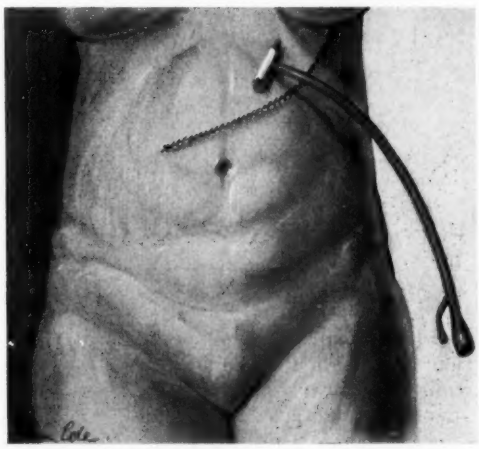

FIG. 1B. Hesseltine clamp in place.

TECHNICAL CONSIDERATIONS IN MANAGEMENT

Gastrostomy was successful in man only when the visceral and parietal peritoneal surfaces were carefully sutured with silver wire by Verneuil [17] in 1876.

Fusion of the visceral and parietal peritoneal surfaces is important to prevent leakage. Dragstedt [3], Dorton [2] and others have suggested that the omentum be interposed between the stomach and abdominal wall as an alternative method for preventing leakage.

When there is a clear-cut indication for the use of this method, the site for the gastrostomy is selected approximately midway between the lesser and greater curvatures at the junction of the middle and lower thirds. A stab wound should be made with a No. 11 blade, preferably smaller than the diameter of the tube, with careful attention to hemostasis. The Foley bag catheter is enclosed by a double purse-string suture, and the balloon is inflated with approximately 7 ml. of water. It should be brought out through a small stab wound in the abdominal wall, and the site of exit should be carefully chosen so that no undue tension or distortion of the stomach will result from traction upon the tube. It is well to suture the visceral and parietal peritoneal surfaces with several interrupted sutures; traction is maintained upon the balloon with a modified Hesseltine umbilical clamp. (Fig. 1A and B.) A larger balloon is not necessary and actually may be undesirable because of its ability to stimulate the antrum with resultant increased gastric secretion.

The management of this tube is different from that of the Levin tube in several respects. Little or no drainage can be expected during the first twenty-four hours and attempts to irrigate the tube will be unavailing. With the patient in a recumbent position, the short tip of the tube, ventrally placed, selectively removes air as it is swallowed by the patient but allows fluid and contained electrolytes to traverse a patent pyloric canal. For the same reason, if fluid is instilled through the tube, it will pool in the lower recesses of the stomach and attempts to aspirate will be unsuccessful.

Although a much larger catheter was employed originally, at the present time it is believed that a No. 16 is entirely adequate. In general, the smaller the diameter of the tube the more prompt will be the closure of the

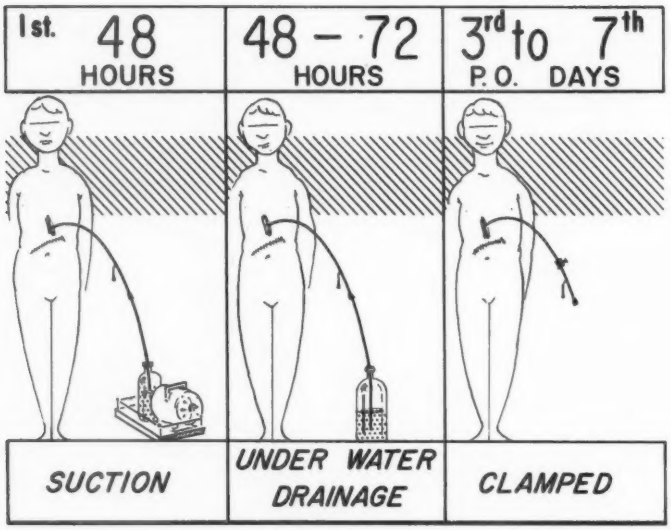

FIG. 2. Postoperative management.

gastrostomy site following its withdrawal. The chief function of a temporary gastrostomy is to remove selectively aggregates of swallowed atmospheric air. The tube should be instilled three or four times a day with 5 to 10 cc. of ordinary tap water to insure its patency.

In other respects the tube is managed much the same as the Levin tube. (Fig. 2.) It is attached to some convenient type of constant suction for a period of twenty-four to forty-eight hours. At the end of this time active suction is abandoned and simple underwater drainage instituted. When this arrangement has been tolerated for another day or two the tube is clamped for observation of physiologic tolerance. As soon as it is clear that the patient will tolerate an oral intake with the tube clamped, it is removed. In early experience in this procedure the catheter was removed on the average of the fourth or fifth postoperative day. However, as experience has increased, the tube has been removed on an average of six or seven days postoperatively. There must be absolute assurance of the patency of the gastrointestinal tract prior to its removal. In vagotomy and pyloroplasty, for example, prior to removal, the fasting stomach is aspirated for residual content in the early A.M., and if the volume is greater than 200 or 300 ml., the tube remains in place. If there is any question as to the patency, it is well to introduce suitable radiopaque substance for roentgenographic examination. It is obvious that prompt closure of the gastrostomy site is contingent upon patency of the gastrointestinal tract and persistent fistulas, when they do occur, are usually a sequel to premature removal.

When these precepts are followed, removal of the gastrostomy tube is usually followed by healing within a few hours.

PHYSIOLOGIC CONSIDERATIONS

The amount of air swallowed with the gastrostomy tube is less than with a nasogastric tube. Dysfunction of the esophageal constrictors and dislocation of the mechanisms involved in deglutition and respiratory exchange actually increase the amount of air entering the stomach. Secretions from the mouth and pharynx are likewise stimulated and entry into the pulmonary apparatus may increase the possibility of atelectasis.

One of the important advantages of this method is selective removal of air as it enters the stomach, allowing fluids to traverse the pyloric canal to physiologic tolerance.

A series of twenty-five patients undergoing vagotomy, pyloroplasty and temporary gastrostomy have been carefully studied. (Table I.) Small amounts of fluids were allowed by mouth from the beginning. During the first postoperative day, this group ingested 690 ml. (with

TABLE I
GASTRIC DRAINAGE IN TWENTY-FIVE PATIENTS

Postoperative Day	Intake (ml.)	Output (ml.)	Balance (ml.)
1	690	598	+ 92
2	652	458	+ 94
3	392	80	+312

adequate intravenous fluids) and the average output was 598 ml. with a positive balance of 92 ml. On the second postoperative day with an average of 652 ml. the gastrostomy output was 458 ml. with a positive balance of 94 ml. During the third postoperative day an average intake of 392 ml. resulted in an output of 80 ml. and a positive balance of 312 ml.

When nasogastric suction is employed, however, the studies of Taylor [*16*] show that suction during a twenty-four hour period, with nothing by mouth, will yield 1.83 L., and when 3,000 ml. of oral intake is allowed, as much as 5 L. will be aspirated. Obviously, this unnecessary removal of large amounts of ion-containing fluid complicates fluid and electrolyte maintenance.

The studies of Gillesby and Puestow [*6*] of fifteen patients undergoing temporary gastrostomy, illustrate this point further. (Fig. 3.) In the same patient, when the use of a nasogastric tube was added to the temporary gastrostomy, the amount of aspirate from the latter site (with the Levin tube clamped) was increased by an average of 750 ml. In one patient the amount of aspirate was increased by 2,100 ml. by the simple presence of a Levin tube. In addition to increased oral and pharyngeal secretions, the presence of a Levin tube will reflexly increase gastric secretion.

TABLE II
COMPLICATIONS REPORTED BY VARIOUS GROUPS

Source of Data	No. of Patients	Complications	
		Major	Minor
Gilchrist 1958	700+	0	Local leaks
Cleveland Clinic 1958	100+	?1	Bleeding
Dragstedt 1958	287	0	Balloon distention
Perlman 1958	400+	0	Persistent fistula
Erlich 1958	25	0	Wound infection
Long Beach V.A. Hospital	400+	0	Intermittent positive pressure breathing
Personal	300+	2	
Spaulding	300+	1	
Total	2,512		

COMPLICATIONS

Through personal communication, data have been accumulated on 2,512 patients in whom temporary gastrostomy had been employed. (Table II.) Information was particularly so-

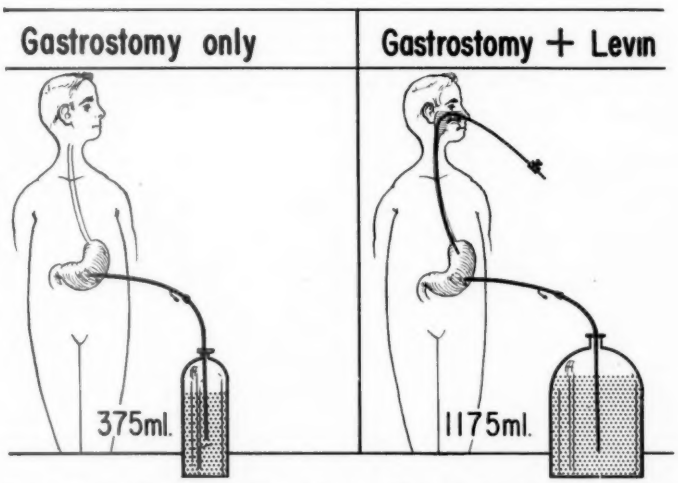

FIG. 3. Twenty-four hour gastric aspiration (fifteen patients). The average increase for those with gastrostomy plus levin was 750 ml. (From: GILLESBY, W. J. and PUESTOW, C. B. *Am. Surgeon*, 25: 927, 1959 [*6*].)

licited concerning the incidence of major complications.

It is apparent that a distressing major complication may rarely occur.

Gillesby and Puestow reported a fatality in a patient who removed his gastrostomy tube while asleep. There was resultant leakage and peritonitis from which the patient expired. In this particular case the visceral and parietal peritoneal surfaces had not been approximated.

Spaulding [*14*], in a series of 300 patients, had three patients in whom leakage occurred requiring re-operation. There were no fatalities.

Hoerr [*8*] reported an elderly, critically ill patient in whom the site of gastrostomy leaked, and may have been a contributing factor in the ultimate death of the patient, although the relationship was not absolutely clear.

Senter [*13*] reviewed fifty-seven patients undergoing temporary gastrostomy and described three fatalities, one a direct result of the gastrostomy and two with a possible indirect relationship. The former (in a patient of ours) occurred as a result of error in management. This patient convalesced uneventfully from vagotomy, pyloroplasty and temporary gastrostomy. The removal of his tube was followed by prompt healing, and prior to discharge, during a paroxysm of coughing, he suffered a wound dehiscence. Following closure, he manifested severe cardiovascular collapse which failed to respond to the usual supportive measures. Autopsy revealed that, apparently, during the secondary wound closure, the stomach had been sheared away from the abdominal wall by a retractor, the gastrostomy site reopened, with resultant chemical peritonitis and septic shock. This is obviously a preventable complication.

Another case of vagotomy and pyloroplasty developed acute obstruction of the small bowel and pancreatitis postoperatively with intraperitoneal leak at the site of gastrostomy and resultant abscess, requiring surgical drainage.

In two patients, during intermittent positive pressure breathing of helium oxygen with the gastrostomy tube closed, there was evidence of minor intraperitoneal leakage manifested by pain radiating to the shoulder. Prompt aspiration of the stomach alleviated the problem and neither developed abscess or required re-operation.

Bleeding from the gastrostomy site as reported by others has not been a problem [*7*].

There have been no persistent fistulas from the gastrostomy site, although early in the course of this experience several patients from whom the tube was removed (frequently as early as the fourth day) had leakage for twenty-four to seventy-two hours. However, since it is now our practice to leave the tube in considerably longer and methods have been adopted to ascertain more critically the patency of the pylorus, this complication no longer exists.

There have been no severe wound infections at the site of exit and, ordinarily, dressings are not required after twenty-four hours.

Most complications of this method may be prevented by attention to technic and postoperative management.

Holder and Gross [*9*] report 187 gastrostomies in infants less than ten weeks of age. Complications were rare. There were no fatalities and only one major complication.

SUMMARY

When prolonged decompression of the gastrointestinal tract is desired, temporary gastrostomy appears to be an acceptable substitute for nasogastric suction. It obviously should be used with care and with clear-cut indications.

Holder and Gross state: "It is our clinical impression that the more liberal use of the temporary gastrostomy in babies is the most significant single improvement made in this institution in the past few years in the general care of the small surgical patient."

It is impossible to evaluate the decrease in morbidity or mortality in adult patients with whom this method is used. We are convinced, however, that in certain poor risk patients the use of this method has been a critical consideration in the ultimate recovery of the patient.

Although certain distressing complications have occurred, it would seem that with attention to operative technic and postoperative management, they may be minimized.

When prolonged decompression of the gastrointestinal tract is desired, particularly in the poor risk patient, serious consideration should be given to employment of temporary gastrostomy. We believe it will continue to occupy a definite place in the armamentarium of the general surgeon.

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DISCUSSION

Herbert S. Movias, II (Long Beach, Calif.): I have never been considered the epitome of brevity, but I shall try to embark toward that reputation today. It should be easy, for Smith and Farris have comprehensively and honestly presented their paper, "Temporary Tube Gastrostomy." This task, I believe, was incumbent upon the authors, for they were responsible for introducing the procedure here in the West. And, as we all know, complications have developed demanding reevaluation. Their facts and their reasons for favoring tube gastrostomy have been presented, and I am in complete agreement.

I am quite certain that those who have used tube gastrostomy are convinced it is infinitely more comfortable for the patient than a nasogastric tube. Therefore, if it can be accomplished without any greater risk of complications than might result from using nasogastric suction, it obviously should be the procedure of choice.

At the Long Beach Veterans Hospital it has been used extensively for over five years, without a single serious complication. Therefore, I am convinced it can be safe, if the technic, as outlined by the authors, is carefully carried out.

If this procedure can reduce the rate of complications resulting from postoperative gastrointestinal decompression, that lends more weight to its superiority. I believe it can, and I therefore again agree with the authors.

I have some misgivings about agreeing with its use in portacaval shunts and aneurysms. Innocuous as it may seem, any possible enterogenous contamination of the operative field, in what otherwise is a clean operation, may introduce infection that could be serious. My only regrets regarding tube gastrostomy have been in two such cases; technical errors were made in each case although not at the Veterans Administration Hospital. I will prognosticate that after further experience with eliminating gastric decompression after vagotomy and pyloroplasty, the authors will return to tube gastrostomy. At Long Beach Veterans Hospital we have run the gamut, and always return to decompression. I am certain tube gastrostomy will continue to be used, and with more understanding and safety.

R. Bruce Henley (Oakland, Calif.): During the past few years, Dr. Edwin G. Clausen and I have rarely used nasogastric suction or any other form of decompression in the postoperative management of our elective gastrointestinal cases. This includes those patients upon whom resections of the stomach, small and large intestine and rectum have been performed.

This type of management of course is not new. Metheney and Lundmark of this association reported their series in 1955. Our fellow members, Sprong and Pollock, presented a paper before us in 1957 indicating that postoperative nasogastric suction had not been necessary in a series of patients undergoing subtotal gastrectomy and cholecystectomy.

Recently we have adopted this type of manage-

ment with a group of patients undergoing hemigastrectomy and vagotomy and pyloroplasty and vagotomy. There are sixty-four patients in this series, thirty-one with pyloroplasty and vagotomy and thirty-three with hemigastrectomy and vagotomy without any form of postoperative decompression.

The volumes of gastric secretions found in thirty-two patients on the morning of the fourth postoperative day when a nasogastric tube had been inserted for purposes of measurement are as follows: 10 to 50 cc. in eighteen patients; 50 to 100 cc. in six; 100 to 150 cc. in four; 150 to 200 cc. in one; 200 to 250 cc. in two; and 450 cc. in one. The last patient had undergone hemigastrectomy and vagotomy. Sixteen of these thirty-two patients had undergone pyloroplasty and vagotomy. In the other sixteen, hemigastrectomy and pyloroplasty had been performed. There was no difference in the amounts of gastric secretions found to result from these two operative procedures.

There have been no immediate or delayed complications following this type of management. All of these patients were discharged seven to nine days after surgery.

Our studies in this small group of patients without decompression would lead us to agree with the authors that the nasogastric tube increases the oral and pharyngeal secretions and reflexly stimulates the stomach with resultant increased gastric secretions.

We wish to congratulate the authors on their excellent re-evaluation of the use of temporary gastrostomy. They have clearly pointed out the situations in which this procedure is indicated and likewise have shown that there are many instances when postoperative decompression is not necessary.

Within our limited experience in employing temporary gastrostomy for prolonged decompression, we agree with the authors that one of the chief indications for its use is in patients with concomitant pulmonary and cardiac disease and in infants.

David Metheny (Seattle, Wash.): I particularly enjoyed Gordon Smith's paper today and his revaluation and simplification of the technic which he uses, but I do wish to talk about the nonuse of suction in vagotomized patients.

Dr. Lundmark and I have not been using routine gastric suction for the last ten years. If a patient has no distention when the surgeon has completed his operation, and he believes that the mechanics of his operation are satisfactory, we think it is not usually necessary to use gastric suction; this is predicated on the iatrogenic changes in physiology that occur after surgery.

Immediately after any abdominal surgery peristalsis is depressed, and along with this depression of peristalsis is a fall in eosinophil count. As the patient recovers from surgery, peristalsis resumes, and although it can be heard, it is not necessarily effective. The doctor cannot know whether or not this peristalsis is effective until one thing happens, namely, if the patient passes gas by rectum. Until that happens, peristalsis cannot be considered effective.

During this time the amount of fluids that are poured into the intestinal tract are decreased, resulting after operation in an intestine or stomach without fluid or gas in it unless introduced from some other source; however, the surgeon will not have any trouble if he does not put the patient on fluids by mouth until gas passes spontaneously.

We have performed fifty-two vagotomies up to this time and have used one type or another of drainage procedure in which we have utilized postoperative suction just twice. Once was early, when we became a little bit afraid. The other occasion for postoperative suction was in a patient who was an air swallower who gulped it down! We had to put in the stomach tube to remove the air that she was swallowing. The other cases have done very well, and I certainly recommend the procedure to you.

However, there is one little thing I would like to add. If, after you have completed your operation, the patient starts to vomit, what is the treatment? The treatment is diagnosis, because the patient may be vomiting from morphine reaction or an intestinal obstruction that has nothing to do with the original operation. However, if you do have to put a tube down, I would recommend that you get a little bit of silicone and rub it on the tube before passing it, then it will not stick to the mucous membrane of the nose or the throat as much and will be very much more comfortable than otherwise.

Edward N. Snyder, Jr. (Pasadena, Calif.): In February, 1957 Drs. Sprong and Pollock, nobly aided by Drs. Lundmark, Joergenson, Ward, Paxton and Farris, with proper ceremony buried the topic of routine use of nasogastric suction. I had hoped that we might do the same today for routine or near routine tube gastrostomy. In cases in which postoperative gastric decompression may seem necessary, gastrostomy is preferable to nasogastric suction but such cases are uncommon.

Like the other discussants, I offer as a substitute for gastric decompression, complete rest of the gastrointestinal tract. As the others have mentioned, this can be utilized successfully in almost any patient with mechanical intestinal obstruction (after surgical relief of the obstructing mechanism) or paralytic ileus from any cause; yes, even from a perforated appendix with generalized peritonitis.

My associate, Dr. Crumrine, and I use a routine similar to that advocated by Dr. Lundmark and Dr. Henley. We pass a Levin tube on some of the

gastric surgery patients and on all patients with a presumtive diagnosis of intestinal obstruction or perforated viscus before surgery, and the tube is connected to active suction until the time of operation. The tube is usually allowed to drain by gravity during the operation, and upon completion of the procedure or when the patient leaves the recovery room, it is removed. The patients are forbidden all oral intake from the time of surgery until they have active bowel sounds and are actively passing gas per rectum. This greatly simplifies postoperative care for the doctor, nurses and patients.

For those of you who are still skeptical, here is a little bibliography that might tempt you to try this technic. First, I would like to refer you to Alex Gerber's article which appeared in *J. Pediat.* in 1955 in which he showed, as others had before him, that air is swallowed in most patients only with deglutition of food or drink. Likewise, I would like to refer you to the paper he wrote with Dr. Frank Rogers and Dr. Lewis Smith that appeared in *Surg. Gynec. & Obst.* in 1958 in which they reported over a thousand cases of individuals treated without decompression of any type and without significant ill effects.

Then that well known internist from Yale, Dr. John Peters, gave a paper that some of you men probably heard. It was delivered at the American Surgical Association Meeting in St. Louis in 1940. The topic was *The Structure of the Blood in Relation to Surgical Problems* and was published in *Ann. Surg.* in 1940. He emphasized the point that many, if not most cases of electrolyte imbalance are iatrogenic in origin. If I may quote from him, he said, "Distention and vomiting, either before or after operation, may often be allayed or checked by resting the gastrointestinal tract as completely as possible. *Complete rest is most easily achieved by withholding all food and fluid by mouth.* If drainage by tube or lavage is instituted because this course, or the courage of the physician fails, care should be taken that as little fluid as possible is introduced, and that should be isotonic with the blood serum."

And finally there is the paper that was written by a gentleman from Portland named W. C. Foster, which appeared in the *J. A. M. A.* in 1928. He demonstrated, rather conclusively, at least I think so, that after division and inversion of the ends of the small bowel, if a dog is fed or given fluids it vomits profusely and dies within a few days of severe electrolyte imbalance. If, however, that dog is deprived of all oral intake, vomiting ceases and the dog lives as long as a dog unoperated on but similarly starved, both dying within three to four weeks.

It seems ironic for me to be urging Drs. Farris and Smith to abandon decompression, because Jack was the first to point out to me that one could perform major abdominal surgery without nasogastric decompression or suction.

Gordon Knight Smith (closing): Dr. Farris and I have no fight with those who do not believe in routine decompression of patients following gastrointestinal surgery nor do we advocate its use. We do believe, however, that certain indications exist in patients undergoing gastrointestinal surgery which make some form of decompression mandatory. Wangensteen definitely proved that, unless atmospheric air is excluded from the gastrointestinal tract in animals with a low ileus, they will die of distention.

Withholding all fluids by mouth, following major operative procedures is very uncomfortable for the patient and at times almost inhumane. I can remember seeing one of our colleagues at that great institution known as "elsewhere" who had had a gastric operation several days before our visit. He was lying in bed with a Levin tube on the table beside him. He was sucking a little piece of lemon and was quite distended. He said: "I finally prevailed upon them to take this tube out of my nose yesterday. It has been down for three days. Now, they won't give me even one sip of water. I wish I had stayed at home." Sprong, Metheny and Henley of this association, as well as others, have written about the use and abuse of decompression. Movius pointed out in his discussion that at the Veterans Hospital in Long Beach they have run the gamut in treating patients with and without decompression. Many patients with chronic duodenal ulcer are aerophagic and, consequently, will swallow air to the point where they become enormously distended. Decompression in these patients, as well as in patients with intestinal obstruction, may well be life saving.

Dr. Farris and I feel very distinctly that, if gastrostomy is performed carefully, with the proper selective indications, it is just as safe if not safer than ordinary nasogastric suction, particularly in the chronically ill patient.

Surgical Treatment of Ulcerative Colitis

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THERE is considerable reluctance on the part of many physicians to utilize the surgeon in the care of ulcerative colitis. The hesitancy dates back to the time prior to the introduction of satisfactory collecting devices and prior to present advances in technic and in supportive therapy. This report will be an accounting of the results of surgical management of eighty-four patients who were treated for ulcerative colitis at The University of California Medical Center, Los Angeles and the Veterans Administration Hospital, West Los Angeles during the past ten years. The cases presented are those in which the author played a personal role in surgical management and procedure, although resident staffs performed the actual operation in about half the cases. The age range was from fourteen to fifty-six years. There was a sex distribution of thirty-four women and fifty men. For purposes of evaluation the tables will show the cases in two groups: patients originally operated upon between 1950 and 1954 are in group I, and those operated upon between 1955 and 1960 are in group II.

SURGICAL TECHNIC

Considerable attention has been given elsewhere to the important phases of preparation of the patient for operation [2]. It is our preference *not* to operate upon a patient receiving steroid therapy but operation is performed if necessary and proper supplementation is added to other forms of preparation. Sulfasuxidine,® supplemented with a twenty-four hour course of neomycin, is the choice for intestinal antisepsis. Purgatives and enemas are avoided. Nasogastric intubation is usually employed. The type of anesthesia is left to the discretion of a competent anesthesiologist: general anesthesia with endotracheal intubation is commonly administered.

The site of the ileostomy is carefully selected with regard for cutaneous scars, the umbilicus, bony landmarks and parietal flexion creases; the stomal incision is prepared through all layers prior to opening the abdomen.

The major abdominal incision is usually a long left paramedian incision. Detailed exploration is performed. The right colon is mobilized first; the terminal ileum is then divided as far distally as possible with due regard for avoiding division in areas of ileac involvement by true ulcerative disease. Traces of edema and dilatation secondary to more distal obstruction may be disregarded. Preservation of as much terminal ileum as possible is important because of the water resorbing abilities of this organ.

A generous segment of ileum proximal to the line of division is then prepared by dividing the mesentery about 1 to 2 cm. from the bowel. (Fig. 1.) This maneuver assures viability of the distal tip. At such a point as to nourish the distal tip of bowel by a major arcade of vessels, the incision in the mesentery doubles back on itself. At this apex, a nonabsorbable suture is placed in the mesentery, next to the bowel wall, avoiding injury to the blood supply to the distal portion. This suture serves for lateral attachment to the peritoneal ring at the point of emergence of the bowel. The mesenteric incision is now carried cephalad in a convex curve laterally, ending at the posterior parietal attachments of the ileocolic mesentery. This curved edge of mesentery will fit into the lateral gutter and close it without distortion of the prestomal bowel. The future stoma should now be drawn through the tunnel in the abdominal wall previously prepared for it. The mesentery is attached to the parietal peritoneum so that it lies lateral to the stoma, thus continuing the plane of the mesenteric curtain into its natural

intersection with the abdominal wall. To secure this mesentery and to reduce the risk of prolapse, it is advisable to suture the cut edge of the mesentery with interrupted nonabsorbable sutures to the parietal peritoneum, beginning at the stoma with the suture previously placed there. In order to assure permanent adherence, an incision may be made in the parietal peritoneum to accept the mesenteric edge.

Once this stage of construction of the ileostomy has been reached, one may proceed with the remainder of the colectomy with the comfortable feeling that the procedure can be terminated quickly at any time if necessary by exteriorization of as much colon as has been mobilized.

In general terms it is preferred to perform a total colectomy in one stage except as follows: (1) where rectal innocence of disease implies possible ileorectal anastomosis, now or later; (2) where extensive anorectal sepsis might seriously contaminate the abdominal wound and peritoneal cavity; (3) in males whose sexual potency might be affected by a bloody dissection in a narrow pelvis in the presence of acute inflammation; (4) in any patient whose general condition does not warrant further operating by the time dissection has come around to the rectosigmoid colon.

Removal of all the colon proximal to the rectosigmoid is urged in the presence of free perforation. Total one stage colectomy may be the only means of controlling bleeding when this has been the indication for operation.

If a two stage procedure is chosen, it is preferable to leave an open mucous fistula to assure external drainage of any active septic process in the distal segment.

During the actual rectal dissection, care is taken to keep the plane of dissection as close to the bowel as possible, especially in the male, to avoid the genitourinary complications of impotence and bladder dysfunction. It is neither desirable nor necessary to remove any portion of the levator ani muscles.

If an ileorectal anastomosis is to be performed Turnbull's technic [4] is followed in detail.

Closure of the wound is usually performed in layers, with the use of nonabsorbable sutures; and in all but the best risk patients retention sutures are used for extra support. If serious contamination has been encountered, as in free perforation, the fascial and peritoneal layers are closed with wire or catgut and the skin and fat are left open for a delayed closure in four or five days.

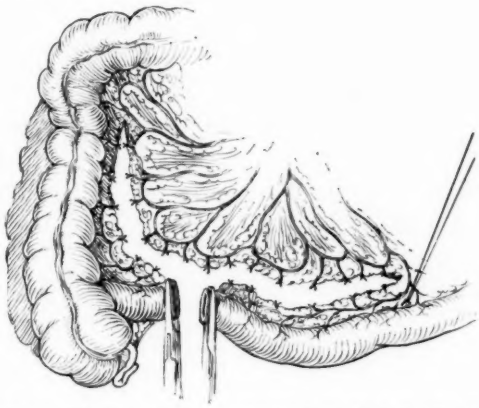

FIG. 1. This drawing shows the level at which the distal ileum is divided, the long vascularized loop of ileum to be brought through the abdominal wall, and the curved incision in the ileocolic mesentery. The suture placed at the angle will be used to attach the ileum to the peritoneum as the bowel emerges from the peritoneal cavity.

The ileostomy is matured immediately by a technic similar to that of Turnbull [3]. Several longitudinal incisions are placed in the distal two thirds of the exteriorized ileum, through serosa and muscularis. This renders the distal portion patulous without devitalizing it, and assures adherence of the everted and scarified layer to the proximal inner layer. A carefully fitted transparent, disposable plastic ileostomy bag is placed on the wound immediately.

The majority of complications encountered in the second half of this series can be directly traced to failure to follow meticulously the principles described above.

OPERATIONS PERFORMED

Table 1 presents a summation of the eighty-four cases. Approximately fifteen other patients were seen during this period. They had received surgical treatment for ulcerative colitis elsewhere and their problem was not currently of a surgical nature.

The one stage total colectomy was the most common initial operation. It was performed in twenty-three of the sixty-six patients operated upon in the last five years. There were three deaths among the thirty-one patients in whom this operation was used in the total period. The two stage total colectomy appears to carry

TABLE I

SUMMARY OF SURGICAL TREATMENT OF EIGHTY-FOUR PATIENTS WITH ULCERATIVE COLITIS

Type of Operation	1950–1954						1955–1960					
	Elective			Emergency			Elective			Emergency		
	No. of Cases	Post-operative Death	Late Death from Any Cause	No. of Cases	Post operative Death	Late Death from Any Cause	No. of Cases	Post-operative Death	Late Death from Any Cause	No. of Cases	Post-operative Death	Late Death from Any Cause
Ileostomy only	1	0	0	0	0	0	0	0	0	0	0	0
Ileostomy, later colectomy (partial)	0	0	0	2	0	0	0	0	0	0	0	0
One stage ileostomy and total colectomy	8	1	2	0	0	0	20	1	1	3	1	1
Ileostomy and staged total colectomy	4	0	0	2	0	0	5	0	0	5	0	0
Ileostomy and partial colectomy	4	0	2	1	1	0	10†	1	0	3	1	1
Anal ileostomy	1	0	0	0	0	0	0	0	0	0	0	0
Ileorectal anastomosis, complementary ileostomy	0	0	0	0	0	0	1	0	0	0	0	0
Transverse colostomy	2*	0	0	0	0	0	2*	0	0	0	0	0
Revision only, original operation elsewhere	1	0	0	1	0	0	5*	0	1	0	0	0
Colectomy only, original operation elsewhere	0	0	0	0	0	0	1	0	0	1	0	0

* One patient in each of these groups has had proximal recurrence requiring ileostomy and right colectomy in one case and ileocolostomy in the other.

† Three of these patients were ultimately treated by ileorectal anastomosis.

TABLE II

INDICATIONS FOR SURGERY AND RESULTS

Indication for Operation	No.	Results 1950–1954			No.	Results 1955–1960		
		Excellent	Fair	Dead of Any Cause		Excellent	Fair	Dead of Any Cause
Elective								
Chronicity (failure to respond to medical care, distant complications, multiple recurrences)	14	8	3	3	36	28	5	3
Bleeding					1	1		
Sepsis (including rectal infection)	2	1	1		6	5		1
Perforations					1*			1
Polyposis	2	1		1				
Stricture (or suspicion of carcinoma)	3	2		1				
Total	21	12	4	5	44	34	5	5
Emergency								
Perforations	2	2			7	5		2
Acute fulminant disease	3	2		1	2	2		
Hemorrhage	2	1	1		2	1		1
Sepsis					1			1
Total	7				12			

* Initial operation elsewhere for this indication. Operation at UCLA Medical Center for stricture.

TABLE III
NUMBER AND TYPE OF COMPLICATIONS

Episodes of Complications	1950–1954	1955–1960
Stomal complications		
Retraction and/or necrosis	6	6
Prolapse	9	2
Fistula	2	0
Stricture	8	5
Proximal perforation 2 degrees to stricture	2	0
Prestomal twist	4	0
Intestinal obstruction due to bands or internal adhesions	7	7
Dehiscence	0	5
Peptic ulceration	1	2
Intra-abdominal abscesses	2	3
Recurrent enteritis	2	4
Neoplasm of colon	2	0
Hepatitis	0	1
Spontaneous ileac perforation	1	2
Septicemia (gram-negative)	1	3
Enteritic (staphylococcal)	0	2
Perineal abscess (major)	2	0
Wound infection (major)	4	4
Spontaneous rupture of spleen	0	1
Septic abortion, pelvic peritonitis	0	1
Severe electrolyte imbalance	0	1
Total gastric erosion	0	1
Malabsorption, severe	0	2
Potassium loss nephritis	1	0
Transfusion reaction, renal shutdown	1	
Total	55	52

TABLE IV
SURGICAL CORRECTION OF COMPLICATIONS

Type of Surgery	1950–1954	1955–1960
Laparotomy (for obstruction, volvulus bands, etc.)	10	9
Closure, dehiscence	0	5
Major local revision	14	11
Minor local revision	15	9
Incision and drainage, intra-abdominal abscess	1	3
Gastric resection for ulcer	0	2
Total	40	39

the lowest mortality risk (no deaths among sixteen patients) amongst the major types of operation. This may be an illusion because of the fact that several of the patients who were subjected only to ileostomy and partial colectomy died before being subjected to the second stage and their mortality is debited to the first operation.

Four patients with what appeared to be left sided colitis were treated initially by transverse colostomy. In two of these patients there has been no proximal recurrence; a third has undergone ileostomy and right colectomy and the fourth has had a resection of terminal ileum with an ileocolic anastomosis.

The over-all mortality risk improved during the second period. There were four deaths among the first twenty-eight patients and four in the second group of sixty-six patients. This gain may be ascribed to many factors but experience and technical improvement must be considered important. There were only two deaths among the last forty-four patients who underwent elective operation. Many of these "elective" operations were performed as urgent operations without optimal preparation, but they could not be placed in a class of true emergencies.

INDICATIONS FOR OPERATION

The indications for operation reviewed in Table II are related to the results.

The general term, chronicity, describes the chief indication for operation. Herein are lumped those patients whose chronic debility or whose recurring episodes of colitis make the compromise of ileostomy and colectomy attractive. Included with this group are a few patients whose distant complications, such as arthritis, were an important factor in bringing them to operation.

The next most common indications are much more imperative: perforation and the acute fulminating form of the disease. There was no clear impression that the results are related to the reason for which the operation was performed.

COMPLICATIONS

The number and type of complications are detailed in Table III. The number of surgical procedures needed to correct the more critical of these complications are described in Table IV.

It would seem unlikely that any surgical operation that is followed by such a catalogue of problems should be widely accepted. Several points should be made regarding these complications to dispel this impression.

Certainly obstruction of the small bowel due to adhesive bands has been one of the most common complications but one which was treated surgically with minimal morbidity. The number and severity of adhesions could in no way be related to the type of operation, the degree of peritoneal contamination or the use of steroid therapy.

It had been our clinical impression that the presence of concurrent therapy with steroids greatly added to the hazards of late complications. This cannot be substantiated statistically, but certainly the majority of complications detailed above are derived from only half a dozen patients, whose complications seemed aggravated by high dosages of steroids. Most specifically related to steroid therapy were three episodes of completely unexplained small bowel perforations in small bowel free of adhesions, trauma or previous apparent disease. Another less clearly defined relationship exists in the enlargement in the stomal hiatus and development of a combination of prolapse, (alternating with retraction) and peristomal herniation, seen most commonly in those patients operated upon under large doses of steroids. This enlargement of the parietal opening has been observed even in those patients in whom care was taken to try to keep the tunnel narrow.

Another serious complicating factor has been the recurrence of enteritis in proximal bowel. This has not always been presaged by recognizable specific ileac involvement at operation. The presence of true local disease of the small bowel, however, has been implicated in several instances of local ileostomy problems, especially those of stricture and fistula.

The early diagnosis of stenosis of the stoma, as indicated by cramps and paradoxical diarrhea, and its ease of correction by a minor surgical lysis of the constricting scar has been described elsewhere [1].

Prolapse, a much more difficult condition to treat successfully, has occurred much less frequently in the more recent series. Major revision, including reattachment of the ileac mesentery to the parietes, shortening of the mesentery and reduction of a peristomal hernia, if present, are the important factors in its treatment.

In this rehearsal of complications one can easily lose sight of several profitable aspects. First, between the two periods there has been considerable improvement in freedom from complications; in the first series only one fifth of the patients were free of complications, while in the second series two fifths were free of all complications. This improvement is in part due to selection of more favorable cases for referral by the internist to the surgeon but is also due in part to the surgeon learning to provide better surgical management. Furthermore, only six patients experienced complications after three years from the date of the original operation, and all these had suffered continuing problems since operation. One might put this differently: after three years have elapsed from time of operation one need anticipate few further problems.

REHABILITATION

With the background of frequent complications of varying severity beclouding the advisability of surgical treatment of ulcerative colitis, it seemed proper to evaluate the results in terms of rehabilitation. The extent of relief that can be given to a patient can be appreciated by answers from the two patients whose results were to the author most discouraging from the point of view of multiple complications and operations. Their case reports are presented briefly below:

Case I. M. F. was operated upon in 1954 because of twelve years of incapacitating bloody diarrhea. His course had been complicated by a transfusion reaction and temporary acute renal failure. Later complications of stricture, prolapse and peristomal herniation following trauma have necessitated a total of eleven minor or major operations. Nevertheless he is actively employed, weighs more than at any other time in his life and avers that he is better able to handle the affairs of his life than at any time since the onset of the colitis.

Case II. M. S. was operated upon in 1950 because of hemorrhage and rectal sepsis. His course has similarly been complicated by prolapses and strictures and a recurrence of an enteritis involving the full extent of his small bowel. Multiple stomal revisions and proximal bowel resections have been necessary, but the patient is presently employed as an electrician, weighs about twenty-five pounds more than at the original operation and states that in spite of the complicated course of his disease he would not hesitate to choose ileostomy again, and indeed wishes it had been undertaken earlier.

This theme of satisfaction was repeated over and over again in questioning the forty-three patients with whom direct contact could be made at the present time. The results of the survey of these forty-three patients, representing two thirds of the living patients, are presented as follows:

Weight Gain. The average weight gain since operation has been twenty-nine pounds, with a spread of from minus twelve to more than eighty pounds. The present weights average one pound greater than the previously recorded highest weights prior to operation.

Occupation. Forty patients denied that their present occupation was compromised by the ileostomy. One patient who was a cook became a salesman; one fashion model bought the dress shop; one woman whose job required lifting heavy bundles of newspapers could not be re-employed. Seven young women have married. There have been at least four children born to the female patients since operation.

Satisfactory adaptation to sexual activity has been reported by most patients of both sexes and in both married and single estate. Impotence has not been encountered in the male patient since our adoption of the technics of rectal dissection described under TECHNIC.

Only five patients admitted any social restrictions. The most common source of complaint was the noisiness of the stomal activity and a limitation of vigorous physical activity by dislodgement of the appliance. Almost all patients, however, have been able to continue swimming, bowling, tennis, dancing and similar activities without inhibition.

Only one patient felt he was less well able to cope with the affairs of his life now than prior to operation; nine felt equally well able and thirty-three felt they were much better able.

Indeed, fourteen patients felt better able to manage their affairs than ever before; eighteen felt equally well able; only eleven did not return an answer or stated that they were less able to deal with life.

It is recognized that most of these are highly subjective responses. Replies from the fourteen patients who later died and which one would expect to be unfavorable have not been included in this tabulation.

Psychologic rehabilitation is another benefit derived from adequate surgical treatment. The so-called "ulcerative colitis personality" does not persist after extirpation of the organic problem. It is clear that in this group of patients there was far more somatopsychic effect observed than psychosomatic.

SUMMARY

In reviewing the experience with eighty-four patients who had ulcerative colitis and who were treated by ileostomy and colectomy, it is apparent that this operative procedure is fraught with many complications and a significant mortality and morbidity. These unfavorable aspects can be minimized by careful attention to detail and meticulous adherence to the surgical principles that have been established during the acquisition of this experience.

In spite of these complications, the end result is an excellent one with regard to rehabilitation. Ileostomy and colectomy can restore a near normal life to the patient with ulcerative colitis; whatever handicaps may exist are gratefully accepted by the patient as a most desirable exchange for the emotional and physical misery and disability which often follow the prolonged conservative, nonoperative approach.

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DISCUSSION

ROBERT A. SCARBOROUGH (San Francisco, Calif.): Dr. Barker has presented a comprehensive report on his considerable experience in the surgical treatment of ulcerative colitis. He has not minimized the complications of surgery, but he has demonstrated that improved technics have greatly reduced their incidence. And he has concluded, rightly I believe, that surgical treatment can cure this disease, with most satisfactory physical and psychologic rehabilitation of the patient.

The significant reduction in morbidity and mortality resulting from surgical treatment during the past ten years can be largely attributed to: (1) removal of the diseased colon as the primary procedure; (2) improved methods of ileostomy stoma construction for prevention of ileostomy dysfunction; (3) improved "collecting devices"

for ileostomy discharge; (4) improved technic of rectal resection for preservation of normal sexual function; and (5) elimination of an open perineal wound by preservation of the external anal sphincter and completion of rectal excision through the anal canal.

Efficient function of the ileostomy stoma is a prime requisite to the success of surgical treatment. There is general agreement that this depends upon the avoidance of both physiologic and mechanical obstruction. Primary union of ileal mucosa and skin is an accepted objective, although there are a number of variations of technic employed.

There are members of this Association who advocate a stoma flush with the surrounding skin and other members who believe that the stoma should protrude for 2 cm. or more above the level of the abdominal wall. Dr. Barker employs a modification of the technic of mucosal graft originally described by Turnbull. We have now abandoned this as an unnecessary procedure, and accomplish a moderate eversion by fixation of the mesentery so that there is a 2 cm. slack in the emerging ileum, with simple interrupted suture of the open end of the ileum to skin.

In preparation for the ileostomy, we excise a square of skin and of anterior rectus sheath to minimize any obstructive compression of the ileum as it emerges through the abdominal wall.

Our technic for ileostomy is also at variance with the generally accepted practice of closure of the lateral gutter. We do not close this space, and assure ourselves of a wide open area by fixation of the mesentery to the anterior peritoneum in a cephalad direction with silk sutures.

I would like to point out that the author's table of indications for operation does not reflect the real danger of development of carcinoma in disease of long standing.

Dr. Barker has made only brief comment upon the recent rebirth of some tempered enthusiasm for preservation of the rectum and ultimate restoration of bowel continuity. Further elaboration on this subject is therefore not warranted in discussion of this paper.

Leon Goldman (San Francisco, Calif.): I am sure that many of you have been concerned in recent years, as we have, about the apparent increase in the incidence of perforation and massive hemorrhage in patients with ulcerative colitis who have received steroid therapy. Dr. Barker, in referring to this phenomenon, mentioned that from his observations it was impossible to prove that a connection existed between perforation and steroid therapy.

As we know, the use of steroids, particularly in patients with acute ulcerative colitis, is becoming more common. In many patients the dosage is increased if they fail to respond initially; therefore, they may receive large doses of steroids often for long periods of time.

We are particularly concerned about the increase in the incidence of perforation because it is difficult to make an early diagnosis of a free or walled-off perforation in patients with ulcerative colitis since steroid therapy masks symptoms.

We reviewed our cases of ulcerative colitis to try to determine whether there was any difference in the incidence of complications in patients who were receiving steroid therapy as compared to those who were not. In this thirteen year period, although these statistics may be interpreted in various ways, the number of patients in both groups is approximately the same. Yet eight patients in the steroid group developed massive hemorrhage as compared to only two in the nonsteroid group. Perforation occurred in eight patients in the group receiving steroids as compared to only one patient in the nonsteroid group. Ten patients developed hypokalemia in the steroid group but no patients did so in the nonsteroid group. Six patients who received steroids developed psychoses, but none did in the nonsteroid group. Four patients developed peptic ulcer in the group which received steroids as compared to only one patient with peptic ulcer in the nonsteroid group.

These statistics seem to indicate that more complications develop in patients who have received steroid therapy for ulcerative colitis.

Lucius D. Hill, III (Seattle, Wash.): Dr. Barker has given a timely and forthright coverage of large experience with a disease which has interested most of us. I would like not only to agree with what he has said about the ileostomy, but to emphasize that we, too, feel that suture of the mucosa of the ileostomy to the skin has been one of the great advances in surgery for ulcerative colitis. But we, like Dr. Scarborough, have abandoned the technic that was originally described by Turnbull in favor of the technic that was described by Brook, namely, simply everting the end of the ileostomy and suturing it to the skin.

We believe that without incising the serosa of the terminal ileum we have had fewer instances of stricture of the ileostomy.

As far as the operative technic is concerned, we have preferred to use a single stage, total colectomy and ileostomy whenever feasible. In this technic we are aided by inserting into the rectum a pack which is soaked in Zephiran.® We tie a tape proximal to this pack. An additional tape is tied to it so that the circulating nurse can remove this from below during the operation. This helps us to define the location of the anus; it also helps in doing the things that Dr. Barker has so aptly pointed out, namely avoiding denervation of the bladder, and also staying close to the rectum to avoid impotence in the male.

After the rectal dissection is complete, the pack is withdrawn from below; the rectal ampulla, a relatively sterile and empty organ, can be opened; the dentate line can be visualized and the entire rectum removed through the abdomen. This saves turning the patient during the operation and performing an abdominal perineal resection, which we believe is a more traumatic procedure.

We have used this procedure in twenty-three instances over the past six years with one death. We have utilized it in some patients on whom we operated as an emergency, and believe that it is only the rare individual who has either extensive pathologic condition of the pelvis, such as endometriosis, or pelvic inflammatory disease, who is not a candidate for this procedure. The only innovations we have been forced to add during the past five years have been those aimed at correcting complications in the posterior wound.

Careful drainage of the posterior wound, scrupulous attention to the posterior wound and digital examination of the posterior wound under sterile conditions insure that there are no loculated pockets of fluid left behind.

WILLIAM H. SNYDER, JR. (Los Angeles, Calif.): In Doctor Barker's extensive series I was interested to note that the youngest patient was fourteen years old. I think this disease usually occurs in older patients. In the November 19, 1960 issue of the *J. A. M. A.* Dr. Kenneth Sawyer reported on several patients having ulcerative colitis, the youngest of whom was seven years old.

Within the last two months we have had two patients in our Childrens' Hospital under the age of five years. In one of these the symptoms began at the age of one and one-half years. At the time we saw the patient, therefore, he had been subject to intermittent bleeding with the usual symptoms of ulcerative colitis for about three years so that it was necessary, because of hemorrhage, to perform a colectomy at this time. We believe, without a large series to back it up, that in this younger age group we should leave the rectum on the possibility of this condition clearing. We do not know the ultimate outcome regarding this younger age group, but I make this suggestion because the problem may be presented to you at any time.

WILEY F. BARKER (Los Angeles, Calif.): I want to thank all of my discussants for their kind remarks.

Let me say quickly that I don't believe the slight differences in technic which have been discussed are significant. I think that the point is that, as has been said in another context, there are many ways of skinning a cat, and if you know how to handle this procedure and know in your own mind how to avoid the pitfalls which your particular technic may expose you to, you will undoubtedly have good results with it.

I might say that in our abstract the comment was made that three fourths of the patients admitted to U.C.L.A.'s hospital ended up having colectomy. This sounds like a dramatically high incidence of surgical attack. This is partly because only the more seriously ill patients have been admitted to the medical services for study. This biases the selection immediately.

But beyond that, we have internists at the U.C.L.A. Hospital as well as at the Veterans Administration Hospital who are surgically minded with regard to this disease. Perhaps the early selection of cases in these last few years has been one of the reasons for there being almost no mention of carcinoma in this series. In the last five years I do not believe we have had a single patient with ulcerative colitis and carcinoma; whereas, in the first five years I believe we had seen several such patients not included in this series because their initial operation had been at another hospital.

We are tending more and more, as Dr. Hill suggested, to do the total colectomy in one stage, with the exceptions that I mentioned for you. And I am perfectly certain that there are several patients who had serious complications but in whom we cautiously chose the subtotal procedure. Two I can think of immediately suffered major bleeding from the distal segment after the initial partial colectomy and probably would have been spared serious morbidity by having had a total procedure performed at the first stage.

The problem of ileorectal anastomosis is a fascinating one. I don't know where we stand on it at this point. I do not think Dr. Turnbull, who is the main advocate of ileorectal anastomosis in this country, is quite willing to come out flatly and say what the role of this operation is. We, with Dr. Clarke at the Veterans Hospital, have had experience with perhaps eight cases of ileorectal anastomosis, and that is a subject for another day's discussion. I think it is something which should be considered further, but I am not willing to accept it wholeheartedly yet.

Regarding Dr. Snyder's comment about our youngest patient being fourteen; this is almost chance. Of course there are no veterans under fourteen, but the exclusion of pediatric patients has been an almost chance occurrence rather than resulting from any other kind of selection.

Gallstones and Diabetes: An Ominous Association

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ALTHOUGH "there is no substitute for technical excellence in surgery" [1], it has been the improved management of associated and complicating disease processes that has been largely responsible for surgical progress in recent years. Thus, fear of complications from sepsis and cardiovascular, pulmonary, hepatic and renal lesions no longer deters necessary and corrective surgery to the extent that it once did. Diabetes mellitus has also been so categorized. A number of recent reports emphasize that mortality and morbidity following elective, planned or nonemergency surgery in the diabetic patient is at little variance from that in the nondiabetic patient [2–4].

On the other hand, disease processes productive of, or associated with sepsis are commonly considered to be more lethal in the diabetic patient; this, notwithstanding the advent of antibiotics. Specifically, that diabetes mellitus adds to the hazard of complications of cholelithiasis is an opinion shared by many. In view of the paucity of information supporting this hypothesis, the present study of this current relationship was undertaken.

PATIENT ANALYSIS

Consecutive patients at the Los Angeles County Hospital, admitted to the University of Southern California Diabetes Service from January, 1953 to January, 1958 and to the services of General Surgery and Medicine from January, 1956 to January, 1958 for the management of cholelithiasis and its complications were surveyed. This survey yielded a total of 481 patients with 626 hospital admissions for analysis. Of these, eighty-six were diabetic patients with 108 admissions and 395 were nondiabetic with 518 admissions. The differential between patients and hospital admissions is represented by fifteen diabetic patients admitted two to three times and ninety-four nondiabetic patients admitted two to five times. Subsequent mortality and operative complication rates reported here, unless otherwise specified, are based upon the number of hospital admissions rather than the number of patients. This concept not only is justified but preferable, since those patients having a prior hospital admission had their disease treated on that admission by a specific method. For example, a patient treated conservatively for acute cholecystitis and subsequently readmitted for elective cholecystectomy should not have his first hospital admission ignored since it represented successful management of a disease process by one type of treatment.

In Table 1 gross mortality for the two groups is tabulated. Twenty patients (19 per cent) of the 108 diabetic and nineteen patients (4 per cent) of the 518 nondiabetic admissions died during management of their disease. Noteworthy is the fact that but thirteen (12 per cent) of the diabetic and ninety-three (18 per cent) of the nondiabetic patients entered the hospital for elective, nonemergency management. Among these patients, but one death occurred; this was a sixty-five year old diabetic woman who died from complications on the sixteenth day after her operation and subsequent to anticoagulant management of thrombophlebitis.

The remainder of the admissions, ninty-five (88 per cent) of the diabetic and 425 (82 per cent) of the nondiabetic, were for complications of cholelithiasis. These complications consisted of acute cholecystitis, pancreatitis, cholangitis

TABLE I
MORTALITY IN DIABETIC AND NONDIABETIC HOSPITALIZED PATIENTS

Admissions	Diabetic*			Nondiabetic†		
	No.	Deaths	Per cent	No.	Deaths	Per cent
Total admissions	108	20	19	518	19	4
For elective surgery	13	1	8	93	0	0
For emergency management	95	19	20	425	19	4
Nonoperative management	60	8	13	318	8	3
Operative management	35	11	31	107	11	10
Cholecystectomy	17	6	35	87	4	4.6
Cholecystostomy	18	5	28	20	7	35

* Fifteen of eighty-six diabetic patients were admitted two or three times.
† Ninety-four of 395 nondiabetic patients were admitted two to five times.

and/or obstructive jaundice. It is to this group that most of our attention is directed since sepsis was commonly involved. Nineteen (20 per cent) of the ninety-five diabetic and nineteen (4 per cent) of the 425 nondiabetic admissions, so categorized, terminated fatally.

In the diabetic group, the type of management selected had but moderate effect on mortality. Eight deaths (13 per cent) occurred in sixty diabetic admissions treated without operation, while eleven deaths (31 per cent) occurred in thirty-five treated with operation. In this operative group the type of surgery performed did not appreciably influence mortality. Thus, six (35 per cent) of seventeen diabetic patients undergoing cholecystectomy and five (28 per cent) of eighteen undergoing cholecystostomy died.

In contrast to the diabetic, rather significant variation in mortality is noted in nondiabetic patients subjected to different forms of management. Eight deaths (3 per cent) occurred in 318 nondiabetic patient admissions treated without operation, while eleven deaths (10 per cent) occurred in 107 admissions treated with surgery. To suggest that these data imply that nonoperative is superior to operative management is not justified since the latter group represents the more severely ill. This is clearly substantiated by the observation that cholecystostomy, the lesser operative procedure, was associated with a mortality almost eightfold greater than that associated with cholecystectomy; seven (35 per cent) of twenty in contrast to four (4.6 per cent) of eighty-seven patients.

The major factors responsible for death in the two groups are tabulated in Table II. No significant differences are to be noted; the same factors producing death are to be found in both groups. However, cognizance should be taken of the fact that infection was responsible for eight deaths among but eighty-six diabetics in contrast to eleven deaths among 395 nondiabetic patients. This represents a threefold greater incidence of infection among the diabetic patients. Deaths due to heart disease were also significantly greater among the diabetics.

The influence of age on mortality in this study is consistent with that observed in other

TABLE II
DEATH IN DIABETIC AND NONDIABETIC HOSPITALIZED PATIENTS

Cause of Death	Diabetic	Non-diabetic
Cholangitis	3	4
Septicemia	3	2
Peritonitis	2	3
Subdiaphragmatic abscess	0	2
Heart disease	4	2
Perforated or bleeding peptic ulcer	3	2
Cardiac arrest	1	0
Pulmonary embolism	1	1
Postoperative hemorrhage	1	0
Cavernous sinus thrombosis	1	0
Carcinomatosis	1	0
Acute pancreatitis	0	1
Uremia	0	1
Cerebrovascular accident	0	1

TABLE III
EFFECT OF AGE ON MORTALITY IN DIABETIC AND NONDIABETIC HOSPITALIZED PATIENTS

Age (yr.)	Diabetic			Nondiabetic		
	No.	Deaths	Per cent	No.	Deaths	Per cent
50 and under	27	1	4	290	1	0.3
51 to 65	32	6	19	88	1	1.1
Over 65	49	13	27	140	17	12

TABLE IV
INFLUENCE OF JAUNDICE ON MORTALITY IN DIABETIC AND NONDIABETIC HOSPITALIZED PATIENTS

Jaundice	Diabetic			Nondiabetic		
	No.	Deaths	Per cent	No.	Deaths	Per cent
Present	15	6	40	57	7	12
Absent	71	14	20	338	12	3

reports [5]. A steady increase in mortality paralleled increasing age in both groups. Whereas the average age for the entire group of diabetic patients (sixty-one years) was appreciably greater than that for the nondiabetics (forty-nine years), the average age of those that died was reversed, namely, sixty-eight years for the diabetic and seventy-seven years for the nondiabetic. On initial inspection it might be suspected that the average age difference of twelve years (forty-nine to sixty-one) was in large part responsible for the greater mortality among the diabetics. However, when adjustments for age are tabulated (Table III), such is found not to be the case; the lethal influence of diabetes upon complications of cholelithiasis is sustained throughout all age groups.

It has been noted in the evaluation of many disease entities that the predominant share of mortality is contributed by patients over the age of sixty-five. Conversely, in such reports, rather few deaths occur in patients under the age of fifty. Between these extremes lies an intermediate or transition age zone which frequently permits a more sensitive appraisal to be made. For example, the influence of specific therapy or the effect of an associated disease may be more critically evaluated in this zone. Table III clearly demonstrates the value of this approach. Whereas the mortality for nondiabetics between the ages of fifty-one to

TABLE V
EFFECT OF CHOLEDOCHOSTOMY ON OPERATIVE MORTALITY IN DIABETIC AND NONDIABETIC HOSPITALIZED PATIENTS

Operation Performed	Diabetic			Nondiabetic		
	No.	Deaths	Per cent	No.	Deaths	Per cent
Yes	16	4	25	50	2	4
No	16	3	19	130	2	1.5

TABLE VI
NONFATAL POSTOPERATIVE COMPLICATION RATES IN DIABETIC AND NONDIABETIC HOSPITALIZED PATIENTS

Type of Complication	Diabetic*		Nondiabetic†	
	No. of Patients	Per cent	No. of Patients	Per cent
Total complication rate	19	53	40	21
Infection	13	36	26	14
Wound	6	17	12	6
Other (e.g., pneumonitis, pyelonephritis)	7	19	14	7
Cardiovascular	2	6	1	0.5
Miscellaneous (e.g., pancreatitis, postoperative bleeding, atelectasis, dehiscence)	4	11	13	7

* A total of thirty-six diabetic patients survived surgery.
† A total of 189 nondiabetic patients survived surgery.

sixty-five was but 1.1 per cent, that for diabetics was 19 per cent.

Although other reports indicate an increased incidence of jaundice in the diabetic with cholelithiasis [6], this difference was not appreciable in this series; fifteen (17 per cent) of eighty-six diabetic and fifty-seven (14 per cent) of 395 nondiabetic patients were jaundiced. As would be anticipated (Table IV), jaundice was associated with an increased mortality in both groups. Six (40 per cent) of the fifteen diabetic and seven (12 per cent) of the fifty-seven nondiabetic jaundiced patients died. These values are in contrast to mortality in the nonjaundiced patients; fourteen (20 per cent) of seventy-one diabetic and twelve (3 per cent) of 338 nondiabetic patients died.

Exploration of the common bile duct in patients undergoing cholecystectomy was required twice as often in the diabetic patients; 50 per cent as contrasted to 28 per cent. Choledochostomy, however, did not significantly alter mortality from that for the entire series: 25 per cent in the diabetic and 4 per cent in the nondiabetic. (Table V.)

Nonfatal, postoperative complications were inordinately high in both groups, but predominated in the diabetic. Fifty-three per cent of the diabetics and 21 per cent of the nondiabetics experienced some complication. (Table VI.) Infection, in one form or another, was responsible for about two thirds of these complications in each group, but in view of the above percentages listed, was two and one-half times more common in the diabetic group. As would be anticipated, cardiovascular complications also were higher in the diabetic patients.

COMMENTS

Interpretation of the data presented here must be correlated with the indigent population served by the Los Angeles County Hospital. A great number of these patients postpone hospitalization until their disease develops severe and prolonged symptoms. Thus, 88 per cent of the diabetic and 82 per cent of the nondiabetic admissions reported here were for emergency rather than elective management. This, in part, accounts for the high mortality and morbidity rates presented. Further, in the nondiabetic group the great proportion (90 per cent) of deaths occurred among patients over the age of sixty-five. While this series cannot be compared directly with a similar evaluation of noncharity patients, certain conclusions appear warranted.

Mortality in disease of the biliary tract is significantly greater in the diabetic than in the nondiabetic patient. Or stated in a converse manner, diabetes mellitus adds greatly to the gravity of complications of cholelithiasis. The over-all mortality in the entire series was fivefold greater in the diabetic (19 versus 4 per cent). And, within the critical or transition age zone, fifty-one to sixty-five years, mortality among the diabetic patients was nearly twenty-fold greater than in the nondiabetic (19 vs. 1.1 per cent). This is the sensitive age area in which the greatest significance of the lethal influence of diabetes upon complications of cholelithiasis is identified. However, even in the geriatric patient, mortality for the diabetic patients remained over twice as great as for the nondiabetic. Mortality in both groups was contributed almost exclusively by those patients over fifty years of age who were admitted for emergency management of acute complications of cholelithiasis.

In contrast, there was negligible risk in those patients, both diabetic and nondiabetic, who sought elective, planned management of cholethiasis by cholecystectomy. There were no deaths among the ninety-three nondiabetic and but one among the thirteen diabetic patients so managed. This single death does not permit significant statistical comparison, but when contrasted to the high mortality rate in the entire series, is sufficient to attest to the relative safety of elective surgery.

It is patent that there is need for a judicious, aggressive approach to the management of cholethiasis in the diabetic. We submit that this aggressive approach should include two basic policies in management. The first recommended policy is that early cholecystostomy, commonly performed under local block anesthesia and usually through a limited incision, be utilized more often for acute cholecystitis in the diabetic. Although the data presented in this report cannot be used to completely support this contention, this simple operative procedure effectively halts progression of this disease and permits subsequent definitive therapy under planned, elective conditions. We believe that if this form of treatment had been carried out more frequently among the diabetic patients who were treated either con-

servatively or by cholecystectomy, several deaths would have been avoided. In the conservatively treated group, management was not always sufficiently aggressive; in some of the patients subjected to cholecystectomy, treatment was injudicious in being too aggressive. Management by both of these methods in this series was associated with a mortality in the diabetic not significantly different from that associated with cholecystostomy. This should never be the case. Cholecystostomy has always been reserved for the desperately ill, as was true in this series, and in all reports it is consequently associated with the highest mortality of all forms of management [5]. This contention is supported by the data from the nondiabetic patients in this series. In these patients with predominantly acute cholecystitis, cholecystostomy was associated with a mortality of 35 per cent, while conservative treatment yielded 3 per cent and cholecystectomy a 5 per cent mortality.

It is acknowledged that many patients who have had cholecystostomy will subsequently require cholecystectomy. However, in many, the emergency procedure of cholecystostomy may serve as a definitive operation. This particularly applies to those in the geriatric grouping in whom an absence of residual calculi is demonstrated by postoperative tube cholecystcholangiography. However, prolonged operative time and trauma should not be sustained in an effort to dislodge a firmly impacted cystic duct stone in a critically ill patient. Adequate drainage of this obstructed diverticulum will halt progression of the disease. If a mucous fistula persists, elective cholecystectomy can be subsequently performed.

The second recommended policy enters the controversy regarding prophylactic cholecystectomy [7]. The data collected here clearly support the contention that most diabetics with cholelithiasis should have planned, elective (prophylactic) cholecystectomy. Excluded from this recommendation would be most of those diabetic patients with significant additional concurrent disease and those that are senile. Maximum benefit would consequently be afforded those patients in whom cholecystectomy is carried out prior to their attainment of the geriatric status. A necessary corollary of the above policy would include the recommendation that cholecystography be performed upon all adult diabetics.

SUMMARY

The data supplied by eighty-six diabetic and 395 nondiabetic patients admitted to the Los Angeles County Hospital for the management of cholelithiasis and its complications have been evaluated. Gross mortality was fivefold greater in the diabetic group. Deaths, almost exclusively, resulted in patients admitted for emergency treatment of complications of cholelithiasis. In the "sensitive" age group, fifty-one to sixty-five years, the mortality among the diabetics was almost twentyfold greater than that of the nondiabetics. As a result of the analysis of this data, two policies are recommended for diabetic patients with cholelithiasis. First, early cholecystostomy should be employed more often for acute cholecystitis. Second, prophylactic cholecystectomy should be performed on most diabetics before they attain older age.

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DISCUSSION

Arthur C. Pattison (Pasadena, Calif.): May I open this discussion by asking the authors a question on a probably not too significant sidelight relative to this study? Two of the several characteristics of acute pneumocholecystitis are that the great majority of patients faced with this problem are males and at least one out of three have diabetes. Was this particular form of acute cholecystitis encountered in this series?

Indeed, Drs. Turrill and Mikkelsen have shown that there exists an ominous association between cholelithiasis and diabetes. With a mortality from elective procedures in the diabetic being over twice that of the mortality for both elective and

emergency surgery in the nondiabetic and with an over-all mortality six times greater in the diabetic, I find it impossible to disagree with either of the two policies propounded.

I, too, feel that cholecystotomy should be performed more frequently and also earlier in the diabetic with acute cholecystitis. Aggressive measures to adequately control the diabetes are of course indicated, and if there are questions concerning accurate diagnosis, this can usually be answered by emergency intravenous cholecystogram.

The authors have not eliminated cholecystectomy as an acceptable procedure, and rightly so. However, I believe cholecystectomy should be reserved for the well controlled patient who has, anatomically, a gallbladder that can be removed with minimal dissection and trauma.

It has been made obvious that, whenever possible, operations upon the biliary tract are best performed during intervals of freedom from symptoms of cholecystitis and during control of diabetes. Actually this is not new, for Joslin,* twenty-four years ago, said, "To diabetic patients my advice is to have the gallstones removed when conditions of time, place, surgeon and physician are all propitious." Apparently in too many instances we have neglected to follow this advice. However, referring again to Joslin,† in 1936 he, in collaboration with others, reported on 2,415 deaths in diabetics, with only eleven being due to gallbladder disease. It would be interesting to know, and I cannot find statistics on this point, the percentage of diabetic patients who die in whom gallstones are found at autopsy but who have never had symptoms precipitated by the stones. Certainly it is true that when the silent gallstone speaks in a diabetic it is usually with a very loquacious roar. So at least for the present this proposed policy of agressiveness in the approach to the problem of gallstones in the diabetic should be accepted.

The transition age group referred to by the authors is an interesting and dangerous period. To fully appreciate its significance, I believe it is essential to realize the incidence of cholelithiasis in the diabetic. Lieber,‡ from a study of autopsy material on 1,259 diabetics found gallstones in 381, an incidence of 30.2 per cent. He also found a progressive increase in the incidence of gallstones occurring in each age group beyond the third decade in both female and male patients, white and colored. In diabetics beyond fifty years of age, gallstones were present in approximately one of every two white women, one of three Negro women, one of every five white men and one of every seven Negro men.

Warren* found gallstones at autopsy in 31 per cent of diabetics over thirty years of age and in only twenty-one per cent of nondiabetics over thirty years of age. I cannot help but wonder what the incidence of gallstones is in the Mexican woman who has diabetes, as Dr. Edmonson at the Los Angeles County Hospital has found the over-all autopsy incidence of gallstones in the Mexican woman over fifty years of age to be 40 per cent.

Incidently, there is no published report that I know of in which an author supports the thesis that diabetes favors the formation of gallstones, although it is well known that the liver of the diabetic is particularly susceptible to fatty infiltration and consequently dysfunction from disturbance in lipoid metabolism.

Be that as it may, can we not, then, add one more policy to those suggested by Drs. Turrill and Mikkelsen? We suggest that the work-up for all diabetic patients include a cholecystogram, and that this roentgenologic procedure be repeated in the diabetic patient at respectable intervals.

HELEN E. MARTIN (Los Angeles, Calif.): This paper points out clearly that vascular accidents and infection are major problems in the diabetic with severe disease of the biliary tract.

The fact that the middle aged and elderly diabetic, and the younger diabetic with diabetes of long duration, have more generalized vascular disease (coronary, cerebral, renal and peripheral) is well known. What is not so clearly appreciated is the frequency of occurrence of vascular accidents following surgery in the diabetic. Precipitating factors may be a fall in blood pressure during anesthesia or secondary to uncorrected fluid losses preceding, during or after surgery and the type of diabetic control. These factors are more apt to be present when surgery is performed on an emergency basis. Furthermore, many physicians cause serious problems by ineptness in handling the diabetic state postoperatively. Due to the stress situation of surgery and use of intravenous glucose, it is difficult to control the diabetes perfectly in the immediate postoperative period and actually it is unwise to attempt this. Good control can be reinstituted easily when the patient is able to eat. All that is necessary postoperatively in the diabetic control is to prevent ketosis, hypoglycemia and undue fluid and electrolyte loss. As it is safer to carry the postoperative diabetic with moderate glycosuria, more intravenous glucose in water and saline will need to be supplied than in the nondiabetic in order to cover the extra loss of water and sodium occasioned by the glycosuria.

* JOSLIN, E. P. Diabetic Manual, p. 150. Philadelphia, 1937. Lea & Febiger.

† JOSLIN, E. P., DUBLIN, F. I. and MOOKS, H. H. Studies in diabetes mellitus. *Am. J. M. Sc.*, 192: 9, 1936.

‡ LIEBER, M. M. The incidence of gallstones and their correlation with other diseases. *Ann. Surg.*, 135: 394, 1952.

* WARREN, S. The Pathology of Diabetes Mellitus, 2nd ed., p. 106. Philadelphia, 1938. Lea and Febiger.

The increased susceptibility of the diabetic to infection is also a well known fact; the factors in the pathogenesis, however, are poorly understood. Treatment of infection in the diabetic must be prompt and adequate in the use of the appropriate antibiotic for organisms (gram negative bacilli and staphylococci) which are often resistant to many antibiotics, and as to drainage of infected areas.

These problems of vascular accidents and infection in the diabetic patient undergoing gallbladder surgery, often on an emergency basis, suggest that prophylactic elective surgery for gallstones in the diabetic should be considered.*

WILLIAM P. MIKKELSEN (Los Angeles, Calif.): This series presented by Dr. Turrill supports the generally held belief that mortality and morbidity following elective surgery in the diabetic is little different from that for the nondiabetic. It clearly points out, however, that this similarity is not sustained in acute abdominal disease. It emphasizes the need for an aggressive approach to the management of acute surgical disease in the diabetic patient.

In the case of acute cholecystitis this aggressive approach, we believe, should be in the form of more radical recommendations for surgery, but which should be carried out through a more conservative type of operation.

The steepening of the slope of mortality among those diabetics in the intermediate age zone of fifty-one to sixty-five years was most impressive to us. This undoubtedly reflects the precocious aging of the vascular tree in these patients. So once again the effect of age on mortality for a disease is identified.

One further point deserves mention. This point concerns the occult nature of hypovolemia that frequently develops in diabetics with acute abdominal disease due to serious water and electrolyte losses. Urinary output in such patients may be misleading. The dextrose diuresis present gives a false impression that adequate renal perfusion is present.

* This discussion was solicited to include the opinion of an internist who is a specialist in diabetes on this subject.

Operative Cholangiography

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OPERATIVE cholangiography during surgery on the biliary tract is a valuable aid to the surgeon in determining the number and location of intraductal stones before exploration of the common duct. After thorough exploration of the common duct in which irrigation, palpation and probing have been completed, performance of a postexploratory operative cholangiogram is an important step in confirming removal of all stones including those in the hepatic radicles and ampullary region before abdominal closure is contemplated [*2,3,8,10*].

Since 1955, operative cholangiography has been carried out routinely at the University of California Medical Center in most patients undergoing cholecystectomy. This procedure is possible because x-ray facilities are available in the operating pavilion as well as experienced technicians working under the direction of both the radiologist and the surgeon [*5*]. The procedure is not unduly time consuming and does not delay the operation [*1,3,7,10*].

There are, however, certain contraindications to operative cholangiography, such as: (1) adequate preoperative intravenous cholangiograms; (2) poor-risk patients in whom the time factor may be important; (3) acute or perforated cholecystitis; (4) presence of indications for a Whipple procedure.

There are definite well known indications for exploration of the common duct. When these are present, choledochotomy with exploration is carried out regardless of cholangiographic findings. The pre-exploratory operative cholangiogram is nevertheless helpful in accurately localizing and enumerating intraductal stones. The ten indications we use for common duct exploration are: (1) history of jaundice or acute cholangitis; (2) history of biliary colic; (3) postcholecystectomy symptoms which may or may not be associated with cholangitis; (4) the presence of jaundice; (5) the finding of a dilated common duct at the time of surgery; (6) palpable common duct stones; (7) large caliber cystic duct and presence of small stones; (8) palpable mass at the choledochoduodenal junction; (9) chronic pancreatitis; (10) abnormal anatomic location of the common duct at the time of surgery.

TECHNIC

In preparing for operative cholangiography, the patient is positioned on the operating table and over a special x-ray cassette tunnel which contains a mobile Potter-Bucky grid. The left side of the patient is elevated approximately 5 inches with foam rubber sponge wedges in order to rotate the vertebral column away from the operative field to be x-ray filmed. The overhead x-ray equipment is then adjusted and a preliminary roentgenogram is obtained to determine the correct exposure technic and proper positioning of the patient. The patient is then anesthetized and draped (the drapings are sutured to the patient's skin to avoid the use of towel clips and clamps which produce radiopaque shadows on the x-ray film).

The surgeon then proceeds with the operation, and after identifying and isolating the cystic duct, he prepares a 50 ml. Luer-Lok syringe by filling it with one part 50 per cent Hypaque® and two parts sterile water. A length of plastic tubing is used to connect the syringe to a curved or angulated No. 18 blunt needle. All air bubbles are eliminated from the system before proceeding.

The cystic duct is tied next to the gallbladder. The No. 18 needle is inserted into the cystic duct distal to the tie; an additional ligature is used to anchor the needle to the cystic duct.

Injections (made slowly to prevent spasms of the sphincter of Oddi) of 5 to 10 cc. of the Hypaque solution (depending upon the size of the ducts) are made with the syringe held verti-

TABLE I
OPERATIVE CHOLANGIOGRAPHY PERFORMED 1955–1960

Time of Cholangiography	No Stones Found (no. of patients)	Stones Found (no. of patients)	Total
Routine cholecystectomy	133	3*	136
Common duct exploration	53	51	104
Total	186	54	240

* Duct explored.

TABLE II
RESULTS OF POSTEXPLORATORY OPERATIVE CHOLANGIOGRAMS

Cholangiograms	No Stones Found (no. of patients)	Residual Stones, Reoperation Needed (no. of patients)
Taken	39 (71%)	0
Not taken	16 (29%)	3 (18.8%)
Total	55	3

cal and above the patient so that all gas bubbles will rise to the top. A single anteroposterior film is taken while the patient is rendered apneic by the anesthetist.

An additional 10 to 15 ml. of the solution is again injected slowly, and the needle is removed; another anteroposterior exposure and a right and left oblique exposure are then obtained by rotating the table. The gallbladder is removed while the film is being developed. At this point, it is important for both the radiologist and the surgeon to view the developed cholangiograms. If the cholangiograms are abnormal and the common duct is explored, postexploratory operative cholangiograms are always taken. This latter procedure is carried out after the "T" tube has been inserted and the patient is placed in the Trendelenburg position so that any gas which is present may rise to the ampullary region of the common bile duct. Twenty milliliters of saline is initially injected to flush gas out of the biliary tree; this is followed by the injection of 20 cc. of Hypaque solution (one part Hypaque to two parts sterile water). An anteroposterior x-ray film is taken with the patient in the Trendelenburg position and another is obtained with the patient in the horizontal position (the patient is apneic during exposure).

RESULTS

From 1955 to 1960 two hundred forty operative cholangiograms were taken at the University of California Medical Center; of these, 136 (56.7 per cent) were performed during routine cholecystectomies. (Table I.) In three cases (2.2 per cent) unsuspected intraductal stones were found and were removed before abdominal closure. Of the remaining 104 cases (43.3 per cent) the common duct was explored and operative cholangiography was performed. Indications for exploration of the common duct in these patients were: jaundice (50 per cent), dilated common duct (33 per cent) and palpable intraductal stones (5 per cent). In the remaining 12 per cent, indications for common duct exploration included pancreatitis; carcinoma of the pancreas; and stricture, stenosis or atresia of the common duct. (Fig. 1.)

Intraductal stones were found in 50.5 per cent (fifty-four patients) of the 107 (104 + 3) total cases. The remaining 49.5 per cent (fifty-three patients) did not have intraductal stones. Five of these patients (4.6 per cent) had hepatic duct stones and stones in the ampullary region. Seven patients (6.5 per cent) of the group had intraductal stones but had a normal sized common duct.

The importance of obtaining a postexploratory operative cholangiogram before abdominal closure cannot be overemphasized [3,8,10]. Postexploratory operative contrast studies were obtained in thirty-nine (71 per cent) of fifty-five patients with intraductal stones. In the sixteen patients who did not have postexploratory operative cholangiograms, three (18.8 per cent) required reoperation at a later date for removal of residual stones. (Table II.) In one instance, interpretation of the postexploratory operative cholangiograms was equivocal, and re-exploration for removal of one residual stone near the ampulla was carried out eight days later.

The value of the operative cholangiogram is in its detection of unsuspected or overlooked intraductal stones [1,4–7,12]. However, errors in interpretation may occur [1,3,4]. Such errors are caused by (1) artifacts and air bubbles; (2) anomalies which cause constriction of the ducts and negative shadows; (3) errors in dilution

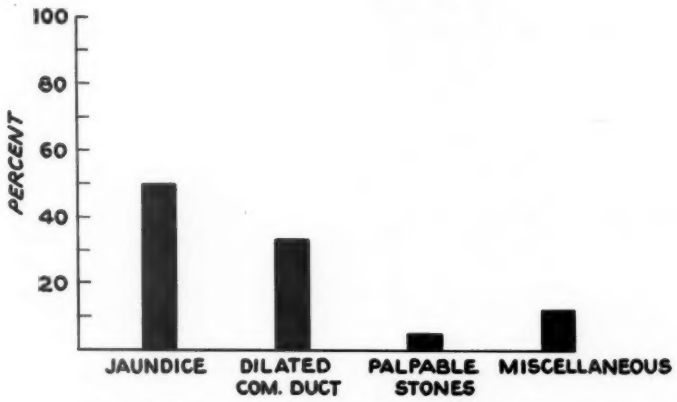

FIG. 1. Indications for common duct exploration in 107 cases.

of dye and evaluation of duct size; (4) overlooked small stones; (5) ductal defects from pancreatitis.

Nevertheless, as our experience in operative cholangiography increased and additional refinements of technic were made, many of the errors commonly encountered in the earlier cases now have been eliminated. Moreover, this procedure has made it possible to visualize stones in the hepatic ducts and ampullary region which otherwise might be overlooked.

COMMENTS

Routine operative cholangiography is probably not necessary in all cholecystectomies, although in three of 136 cases (2.2 per cent) unsuspected intraductal stones were uncovered by such routine studies. An additional four patients with a normal sized common duct harbored intraductal stones, but clinical indications for exploration were present (jaundice, postcholecystectomy symptoms, palpable stones). The many objections to this procedure [3,4,8,9] are based mostly on difficulties in technic, which are easily overcome as experience increases [1,11].

In our series 6.5 per cent of patients with a normal sized common duct had stones. This is in the range comparable to a reported incidence of 5.3 per cent [7].

The most important aspect of common duct exploration is the performance of the postexploratory operative cholangiograms, which most authors advocate [1–4,7,8,10,12]. This is further emphasized by the high morbidity and mortality of secondary operation for removal of residual stones, which is reported to be as high as 21 per cent [8]. In our series, three (18.8 per cent) of sixteen patients in whom no postexploratory operative cholangiography was undertaken required a secondary operation; other authors have reported incidences of 10 to 15 per cent in much larger series [1,6,8,11].

SUMMARY

Two hundred forty cases of operative cholangiography are presented and reviewed. In 136 cases operative cholangiography was performed during routine cholecystectomy, and in the remaining 104 cases it was performed in conjunction with common duct exploration. The technic, which is easy to perform and is not unduly time consuming, is described in detail. The main findings are summarized as follows:

1. Three cases (2.2 per cent) of unsuspected intraductal stones were found.

2. The total mortality rate was 2.9 per cent (seven cases), but in no case was this directly related to operative cholangiography.

3. No morbidity was caused by the procedure itself.

4. Possible errors in interpretation are described. There were three false positives in this series (1.2 per cent), and they occurred in the early part of the study.

5. Of the 107 patients in whom exploratory choledochotomy was performed, stones were found in 50.5 per cent; none were found in 49.5 per cent. It is of interest that in 6.5 per cent of the series (seven patients) intraductal stones were found although the common duct was of normal size.

6. Indications for common duct exploration are described. Dilatation of the common duct was the most frequent indication (50 per cent); jaundice was the next most frequent (33 per cent).

7. The incidence of stones in the hepatic ducts and ampullary region was 4.6 per cent (five patients).

8. Following exploratory choledochotomy in sixteen patients in whom no postexploratory operative cholangiograms were taken, three of the patients required a secondary operation at a later date for removal of residual stones.

9. Routine operative cholangiography is not necessary in all cholecystectomies, but it is of great value in questionable or borderline cases. The most important phase of operative cholangiography after exploration of the common duct is the postexploratory operative cholangiogram which confirms complete removal of intraductal stones and reduces the necessity of secondary operations for removal of residual choledochal stones.

The most important phase of operative cholangiography after common duct exploration is the postexploratory operative cholangiography which confirms complete removal of intraductal stones and reduces the necessity of secondary operations for removal of residual choledochal stones.

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DISCUSSION

Allen M. Boyden (Portland, Ore.): Drs. Gardner, Jew and Goldman have re-emphasized the important benefits to be obtained from operative cholangiography and have advocated its routine use in patients undergoing cholecystectomy. The detailed technic which they described today has been more than satisfactorily demonstrated in a film presented before the College of Surgeons last fall.

Before this procedure can be adopted routinely in one's own practice, it is necessary that the physical setup be adequate to permit accurate results. Without first-class equipment the surgeon will be plagued by indeterminate cholangiograms, false positive and false negative results, and often great loss of time. To be sure, even with makeshift equipment important information may be gained. But, I believe that most surgeons who do not use the method routinely have found it wanting for these reasons. I find myself among this group.

In the review of any series the value of routine operative cholangiography should be evident in three ways. First, it should reduce the incidence of choledochostomy without reducing the percentage of patients from whom stones are recovered. Second, it should disclose unsuspected common duct stones in patients not presenting the usual indications for exploration. Third, it should definitely reduce or practically eliminate the unfortunate finding of residual intraductal stones.

The one most important figure in any review of surgery of the biliary tract is the percentage of patients with common duct stones as compared to the total number of cholecystectomies. There is no doubt in my mind that this figure varies proportionately with the alertness of the surgeon to the well established indications for common duct exploration. I am particularly pleased to find that the authors have closely followed these indications and have not depended solely on operative cholangiograms. The percentage of their finding of common duct stones to total cases is actually 22.5, a most creditable figure, indeed. Although it is not apparent from their paper, I would venture a guess that this percentage would not have been so high had the decision to explore rested solely on the x-ray findings. These fundamental principles must be emphasized continually in the teaching of residents if secondary operations in search of stones are to be reduced. Adherence to these principles has enabled many surgeons to report recovery of similar percentages of intraductal stones without the helpful adjunct of operative cholangiography. The

authors report the pleasant dividend of stone recovery in three patients in whom the usual indications proved inadequate, the cholangiograms giving the only clue to their presence.

Since the indications cannot be absolute, stones are present in only about one half of the ducts explored in most series reported. This percentage should be reduced by operative cholangiography since certain patients with borderline indications (i.e., ducts of 1 cm. diameter in patients without jaundice, palpable stones, evident choledochitis, or pancreatitis) could be eliminated as candidates for exploration. On the other hand, when faced with more positive indications, such as jaundice or definite duct dilatation, I doubt that many surgeons would dare refrain from electing to open the duct because of a negative cholangiogram. As I read the results presented today, the total number of ducts explored was not reduced because of the use of operative cholangiography.

I certainly agree with Dr. Gardner and his associates that the most important part of operative cholangiography is the postexploratory or so-called "completion" cholangiogram. I suspect that most of us have been embarrassed by the occasional finding of residual stones in roentgenograms taken during the early convalescent period. One certain way to avoid such unpleasantness is to follow the ostrich-like practice of one distinguished surgeon I knew. He simply did not take cholangiograms. For the more curious, the percentage of retained stones, even with the most careful surgical technic, reaches 7 to 10. A ten year review at The Portland Clinic, some years ago, showed our figure for residual stones to be 7 per cent.

If only those patients with completion cholangiograms are included, Dr. Gardner and his associates have reduced this figure to 2.5 per cent. However, they prove they are in reality ordinary men like many of the rest of us when they admit to three other instances of retained stones in their total of 55 cases. These were found in the postoperative period when roentgenograms were made of the sixteen patients who had not had completion cholangiograms. The value of the latter procedure could not have been proved more effectively.

We must not expect the postexploration cholangiogram to eliminate completely instances of retained stones. In our own study even postoperative cholangiograms were entirely normal in two patients who later proved to harbor common duct stones which had obviously been missed at operation.

LEON GOLDMAN (closing): We began using operative cholangiography routinely when we moved into our new hospital; we now had the necessary facilities available as well as the cooperation of radiologists and specially trained technicians so that we could perfect the procedure and perform it quickly.

There is no doubt that the surgeon must be willing to spend a little more time to carry out operative cholangiography and he must not hurry the radiologist if he wants to obtain good films and arrive at correct conclusions. When the surgeon first begins to use operative cholangiography, the procedure will take quite a few minutes. After he acquires experience, however, it can usually be completed in ten or fifteen minutes. If he believes that this is too much time to spend or if he is too impatient to wait for fifteen minutes during an operation, then of course he should not consider the procedure.

We found as a result of our experience that some patients had hepatic duct stones which might otherwise have been overlooked. Some patients had normal sized ducts which contain stones, a finding that we had previously not thought possible. We also found, as Dr. Boyden emphasized, that the postexploratory operative cholangiogram was the most important.

As was brought out in the discussion, one certainly would not consider putting a tube in the gallbladder or in the common bile duct and then not obtain a postoperative cholangiogram. However, some surgeons object to doing this at the operating table in spite of the fact that occasionally they have been embarrassed by finding an overlooked stone a week or ten days later; thus, a second lengthy operative procedure is required to remove a small stone that could have been taken out at the first operation if a postexploratory operative cholangiogram had been made.

Trypsin Inhibitor and Proteolytic Enzyme Activity in Dogs after Ethionine-Induced Pancreatitis

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From the Surgical Research Laboratories of the Department of Surgery, University of California School of Medicine, San Francisco, California. Sponsored by the Committee on Research of the University of California School of Medicine, Grant No. 299—Springer.

A TRYPSIN inhibitor was first isolated from pancreatic tissue by Kunitz and Northrup [1]. Later Kalser and Grossman [2] demonstrated the existence of a specific trypsin inhibitor in the pancreatic juice of dogs. These authors [3] also investigated the relationship between this inhibitor and the proteolytic enzymes of the pancreatic juice. In the experiments here reported, pancreatitis was produced in dogs by the administration of ethionine which acts as an antimetabolite to the essential amino acid, methionine. The changes which occurred in the composition of the pancreatic juice were then studied with special emphasis on the activity of the trypsin inhibitor as well as that of the proteolytic enzymes.

METHODS AND MATERIALS

Nineteen mongrel dogs of both sexes, weighing between 14 and 21 kg., were used for these experiments. All the dogs were dewormed and were kept under observation for at least one week before operation. They were then anesthetized with sodium pentobarbital and a laparotomy through a right rectus incision was performed. A modification of the method described by Routley et al. [4] was used to establish an artificial pancreatic fistula with two plastic catheters. The smaller catheter (.042 inches in inner diameter) was introduced into the main pancreatic duct and was secured into place with two silk sutures; the larger (.070 inches in inner diameter) was placed in the duodenum where it was fixed by a purse string suture. Both catheters were then brought out subcutaneously and were joined by inserting the smaller one into the larger one. Thus, the flow of pancreatic juice into the gastrointestinal tract was not permanently interrupted, and easy access to the catheters was still possible for collection of pancreatic juice as desired. A miniature one way ball valve was incorporated in the proximal end of the larger catheter to minimize duodenal reflux into the pancreatic duct system. (Fig. 1.)

Seven days after the above procedure, the animals were lightly anesthetized with sodium pentobarbital. The catheters were brought to the exterior through a small incision in the skin, and an initial sample of pancreatic juice was collected in a container immersed in an ice bath. Subsequently the plastic catheters were rejoined and again placed into the subcutaneous space.

To insure an adequate flow of pancreatic secretion, a solution of 0.9 per cent sodium chloride containing 20 units of secretin* and 20 units of pancreozymin* per 100 cc. was given at a rate of 200 ml./hour during the collection period.

DL-Ethionine† in a daily dose of 50 mg./kg. was given subcutaneously to sixteen dogs. The drug was discontinued two days after the

* Secretin was obtained through the courtesy of Eli Lilly & Company, as well as from Boots Pure Drug Company, Ltd., Nottingham, England. Pancreozymin was also obtained from the latter source.

† DL-Ethionine was obtained through the courtesy of Sigma Chemical Company, St. Louis, Missouri.

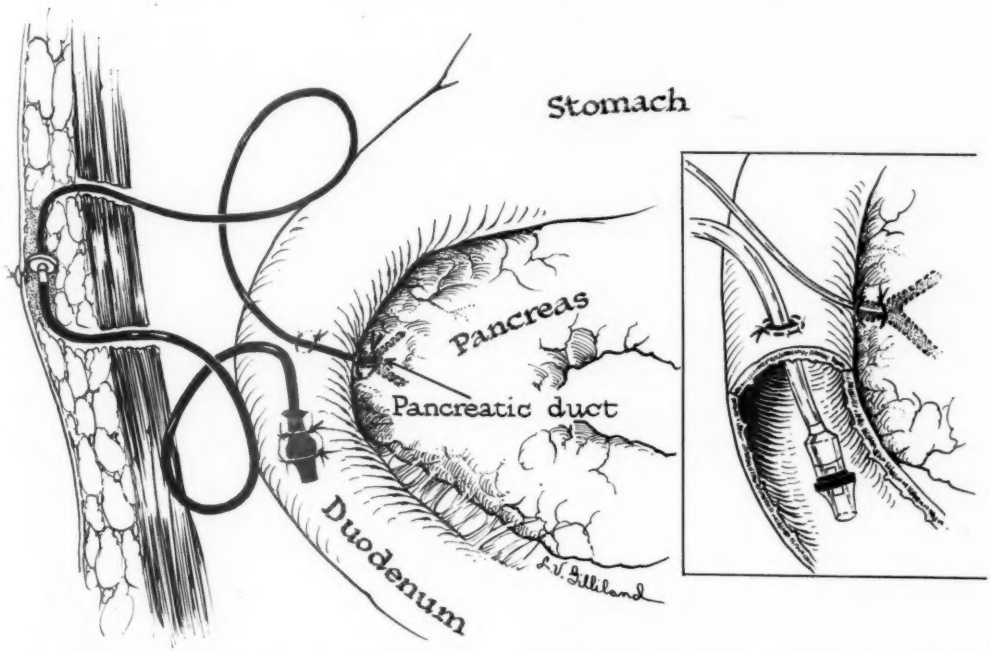

FIG. 1. Subcutaneous pancreatic shunt established by the use of two plastic catheters, one placed in the main pancreatic duct, the other in the duodenum.

animal became anorectic, which usually occurred between the eighth and the twelfth day after administration of the drug had begun. A second sample of pancreatic juice was collected in the same manner as described previously. The animal was then sacrificed, and a specimen of the pancreas was quickly obtained which was immediately fixed in formalin.

Three dogs were used as controls to determine whether the presence of the plastic catheter in the pancreatic duct would produce any change. These dogs received no ethionine but were otherwise treated in the same manner as the experimental animals.

The samples of pancreatic juice were tested for trypsin inhibitor, active proteolytic enzyme and total proteolytic enzyme activity (the latter after activation of the proenzymes). Total nitrogen content, osmolarity, pH and rate of flow of the juice were also determined. The trypsin inhibitor activity of the serum also was measured in five dogs. The determinations of enzymatic activity were expressed in terms of the comparative activity of a standard solution of crystalline trypsin. The trypsin inhibitor was extracted from the pancreatic juice by the method of Kalser and Grossman. Proteolytic enzyme activity was determined by the method of Troll and Doubillet [5] except that the liberated tyrosine was measured colorimetrically with the reagent of Folin and Ciocalteu. The serum trypsin inhibitor was measured by the method described by Christensen [6].

RESULTS

In four dogs no pancreatic juice could be collected after administration of ethionine. At autopsy two of these dogs were found to have extreme atrophy of the pancreas; one had a very severely inflamed pancreas and in the fourth a blood clot blocked the catheter in the pancreatic duct. Consequently, the results as shown in Table 1 were derived from the remaining twelve experiments in which complete studies were obtained.

Pancreatitis of varying degrees was produced in all instances, as evidenced by gross and microscopic examination of the pancreas. The microscopic findings, which were similar to

TABLE I

CHANGES IN THE COMPOSITION OF THE PANCREATIC JUICE AFTER ETHIONINE-INDUCED PANCREATITIS

Dog. No.	Trypsin Inhibitor (units/ml.)		Active Proteolytic Enzymes (μg./ml.)		Total Proteolytic Enzyme Output (μg./hr.)		Flow (ml./hr.)		Total Nitrogen (mg./ml.)		Osmolarity (mOsm./L.)	
	I*	II†	I	II	I	II	I	II	I	II	I	II
1	36	0‡	0.35	156	14,400	1,520	18	8	3.9	0.61	299	344
2	22	0‡	1.1	16.4	112,200	3,000	33	5	0.91	0.71	365	356
3	74	0‡	0.4	13.5	22,000	970	10	9.7	7.3‡	0.31	247	280
4	76	5.2	1.1	14.2	3,300	2,880	30	6	1.26	0.37	431	301
5	88	0‡	0.6	0.63	2,664	1,736	36	8	1.25	0.25	411	334
6	28	0‡	0.3	0.6	13,200	1,476	40	12	1.09	0.38	329	459
7	54.6	7.4	0.72	1.2	5,216	...	32	2	1.41	...	326	...
8	30	2	0.4	36	13,804	3,000	34	3	1.07	1.56	396	147
9	24.7	20.7	0.8	4.5	4,950	18,390	30	6	1.09	1.17	404	246
10	41.8	19	0.6	9.6	5,748	69,600	28	16	1.68	1.17	360	321
11	73.4	0‡	0.7	905‡	5,600	3,832	32	4	1.65	0.42	393	286
12	64.5	0‡	0.5	12.6	10,530	1,320	30	4	2.37	0.97	304	274
Mean	51	10.8	0.63	24.1	17,801	9,793	29.4	7	1.61	0.72	355	304
No. of samples included in mean.....	12	5	12	11	12	11	12	12	11	11	12	11

* Represents control sample (prior to ethionine).
† Represents experimental sample (after ethionine).
‡ Not included in mean.

those reported by other investigators [7,8], included disappearance of zymogen granules, atrophy of the acinar cells, diffuse acute and chronic inflammation and fibrosis of the interlobular connective tissue.

Trypsin inhibitor activity of the pancreatic juice before administration of ethionine ranged from 22 to 88 units/ml. (mean in twelve dogs, 51 units/ml.). After ethionine-induced pancreatitis, trypsin inhibitor activity decreased markedly. In five dogs the inhibitor activity fell to a range of 2 to 20.7 units/ml. (mean 10.8 units/ml.) and in the remaining seven dogs there was no detectable inhibitor activity.

The active proteolytic enzyme content of the pancreatic juice was increased after ethionine-induced pancreatitis from a control range of 0.3 to 1.1 μg./ml. (mean 0.63 μg./ml.) to a range of 0.6 to 156 μg./ml. (mean 24.1) in eleven cases. The increase was marked in nine cases and only slight in two cases. No change was noted in one case.

The total proteolytic enzyme activity, measured after activation of the proenzymes by a standard trypsin solution, was found to be decreased, except for two cases in which an increase occurred. In all but one animal, the production of pancreatic juice was also decreased from a mean control value of 29.4 ml./hour to a mean of 7.0 ml./hour after administration of ethionine.

In addition to the fall in enzyme activity noted above, the total nitrogen content of the pancreatic juice was similarly decreased after administration of the drug, except in two cases in which an increase was noted. The osmolarity of the pancreatic juice was slightly decreased in eight cases and was increased in four cases after administration of ethionine.

Serum trypsin inhibitor activity, which was measured in a small series of five dogs, was found to increase from a mean control level of 1,019 units/ml. to 1,265 units/ml. after pancreatitis was induced.

In the three original control animals, examination of the pancreas did not disclose any gross or microscopic abnormality, nor were any changes noted in the composition of the pancreatic juice when the two samples, collected at a two week interval, were compared.

COMMENTS

The experimental preparation which has been described proved to be very satisfactory for the purposes of this study. It not only provided for ready collection of pancreatic juice with minimal disturbance of the pancreas itself, but it also permitted each experimental animal to be used as its own control, a very desirable feature in view of the wide variation in composition of the pancreatic juice of individual animals.

Ethionine has been used by several groups of investigators to produce experimental pancreatitis [3,7,8]. If given in a sufficient amount, this antimetabolite impairs protein synthesis, presumably by competing with the essential amino acid, methionine, for incorporation into essential intracellular structures. The pancreas is known to be one of the most active organs of the body in protein synthesis. This is indicated by the fact that the pancreas takes up an unusually large amount of labeled amino acids when these substances are given parenterally to experimental animals [9]. Although ethionine also affects other organs active in protein synthesis, such as the liver, kidneys and the small bowel mucosa, the most severe changes occur in the pancreas. This is not surprising in view of the extent to which protein synthesis is required of this organ.

Several investigators have shown that continued impairment of protein synthesis in the pancreas leads to depletion of the zymogen granules, atrophy of the acinar cells, acute and chronic inflammation and finally fibrosis and atrophy of the gland [3,7,8]. These histopathologic characteristics were also observed in the ethionine-treated dogs in this series. Dietary deficiency of protein has likewise been shown both experimentally [10] and clinically [11] to induce functional and microscopic changes in the pancreas. The frequent association of alcoholism with chronic protein deficiency as well as with pancreatitis may therefore be more than coincidental.

The most striking and significant changes in the dogs with ethionine-induced pancreatitis were the decrease or total disappearance of trypsin inhibitor and the increase of the active proteolytic enzyme content of the pancreatic juice. This indicates that the increase in active protease activity as well as the associated decrease or disappearance of the trypsin inhibitor may both be important factors in the etiology of this type of pancreatitis.

The decreases which occurred almost uniformly in total proteolytic enzyme output, in volume and in the total nitrogen content of the pancreatic juice are further evidence of the severe impairment of pancreatic function which was induced by ethionine.

The observation that trypsin inhibitor activity of the serum was not altered by the occurrence of pancreatitis suggests that the inhibitor substance found in serum does not originate from the pancreas. We also noted that serum trypsin inhibitor levels are unaffected by total pancreatectomy in the dog.

CONCLUSIONS

In dogs with ethionine-induced pancreatitis, the trypsin inhibitor activity, total proteolytic enzyme output and hourly volume of pancreatic juice were decreased. However, a significantly larger proportion of the proteolytic enzyme was in the active form.

These findings may provide an explanation for the lysis of the pancreatic tissue itself which is characteristic of acute pancreatitis.

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DISCUSSION

Victor Richards (San Francisco, Calif.): I would like to congratulate Dr. Negulescu and the group at the University of California on this very interesting experiment and the particularly attractive experimental preparation from the standpoint of studying certain parameters of pancreatic physiology.

We ourselves were interested in this about two years ago. At that time I was fortunate to have Dr. Lampros, one of our residents in surgery, become interested in the problem of experimental pancreatitis, and during the year he was with us in the laboratory, we attempted to study trypsin inhibitors, not from the standpoint of the level in the pancreatic juice, such as was done here, but as to the level in the blood stream.

There were two things that we were concerned with. One was, what is the relationship of trypsin to the cause of acute pancreatitis? And, secondly, does the level of trypsin and trypsin inhibitor in the blood have anything to do with the shocklike state which often accompanies acute pancreatitis and which at the present time is still poorly understood?

In order to define the role of trypsin, we decided to prepare for our experiment a little differently. This consisted of opening the abdomen of the dogs, aspirating bile, isolating the main pancreatic duct, ligating it where it enters the duodenum and then injecting 10 cc. of bile into the pancreatic duct as rapidly as we could. This, of course, results in a severe fulminating bile pancreatitis, and, as you know, may think that in man the bile entering the pancreatic duct has etiologic significance in pancreatitis.

We studied the dogs in the acute phase and as best we could in the chronic phase, for most of them died in about a twenty-four to forty-eight hour period. It took about four months to learn how to analyze for trypsin and trypsin inhibitors, so that it is not a very easy experiment.

Here is what actually happened: We cannulated the pancreatic duodenal vein so we could collect the blood from this vein to the pancreas after the injection of bile, and we measured the trypsin inhibitor level. The trypsin inhibitor level in the blood from the pancreaticoduodenal vein started to drop within a period of half an hour and continued to drop progressively until the animal died. We, therefore, demonstrated the progressive fall in trypsin inhibitor level in the pancreaticoduodenal vein until the death of the animal.

The second thing that we did was to measure the trypsin inhibitor level in the peripheral blood, taking a sample from the vena cava. Curiously enough, there was no drop in the peripheral venous blood from the vena cava for a period of at least eight hours, but after eight hours there again occurred a drop in the peripheral vena caval blood, so that apparently there is something taking place that isn't completely related to the pancreas alone in explanation of these findings.

It had been reported that the level of trypsin inhibitor in the blood could be raised in mice by the ingestion of trypsin; therefore, we obtained some crystalline trypsin and fed dogs crystalline trypsin. This resulted in an increase in their trypsin inhibitor level in the blood. We then gave these dogs acute pancreatitis with a higher trypsin inhibitor level in their blood to begin with.

We performed this experiment on only three dogs, and the curious thing is that only one out of the three died. Two of the three dogs survived when they had had a high trypsin inhibitor level to start with. In the other group only two dogs out of fourteen lived. So possibly the level of trypsin inhibitor has some relation to the response to acute fulminating pancreatitis.

There is another aspect of the problem that is probably equally interesting but which we had no chance to study; that is the relationship of trypsin to the fibrinolytic system. As you know, there is a great deal of interest at the present time in these fibrinolysins, and one of the main activities of trypsin is to convert plasminogen into plasmin. Plasmin, of course, is a fibrinolytic agent, and this might have a great deal to do with the systemic reaction which occurs in acute pancreatitis.

By the use of a tagged fibrinogen, which is now available, we should be able to make some fairly accurate studies on the effect of the liberation of plasmin on fibrinogen levels in dogs with acute pancreatitis. We haven't been able to get any significant measurements in man.

We must all be aware that pancreatitis is an extremely different disease when it occurs under different circumstances. Certainly the ethionine-produced pancreatitis might be entirely different from the bile-produced pancreatitis. This, in turn, might be entirely different from the alcohol-produced pancreatitis, and acute pancreatitis, in general, might be different from chronic pancreatitis, which some now think is an expression of an autoimmune disease.

I am very grateful to Dr. Negulescu for bringing these experiments to our attention.

Leon Goldman (closing): I am sure that we are all disappointed in the lack of progress so far in determining the pathogenesis of pancreatitis. It may be that Opie in 1901 provided a disservice by describing the oneway channel and resultant acute

pancreatitis; this concept has formed the keynote of our interpretation of the pathogenesis of this disease ever since. Almost all operative procedures based on Opie's premise which have been devised to treat this disease have met with failure. Sphincterotomy, removal of common duct stones and retrograde pancreaticojejunal anastomoses have not been particularly successful. A metabolic or biochemical approach to the function of the pancreas might eventually improve the results of treatment of pancreatitis.

The method of production of pancreatitis that we used is entirely artificial, as Dr. Richards pointed out, and of course is not exactly comparable to what happens in man. However, ethionine does produce pancreatitis and it does afford the opportunity to study the changes induced by the disease.

We were rather surprised that there was so marked a uniformity in the inhibition of the trypsin content of the pancreatic secretion as demonstrated in these experiments and that there was a drop in the total proteolytic enzyme content, although the amount of active trypsin increased. The volume of pancreatic secretion also dropped and it is very likely that this is part of the mechanism. What triggers the mechanism is not yet clear.

That chronic pancreatitis is a different disease, that it is an autoimmune mechanism, will still have to be proved. The same etiology has been attributed to other diseases although no support for this is yet available.

While we cannot as yet apply the results of these studies in any way, they do afford some information as to what happens to these important substances during pancreatitis, particularly the trypsin inhibitor which, in its reduced state, will allow trypsin to be activated, and this might be an important factor in extensive necrosis.

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Management of Intestinal Atresia at the Los Angeles Children's Hospital

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WE have reviewed nintey-one cases of intestinal atresia (exclusive of esophageal atresia and imperforate anus) operated upon at the Los Angeles Children's Hospital in the period 1937 through 1958. Forty-seven infants (52 per cent) recovered from this anomaly. If we should exclude fifteen cases with such extensive abnormalities as to be incompatible with long term survival, even with ideal surgical correction, the percentage of long term survivors would rise to 62 per cent. (Tables I and II.)

We have used the term "atresia" to denote a complete absence of the lumen in a segment of the intestine or the absence of a segment of the intestine itself. We have not included any cases of stenosis or of obstruction of the diaphragm type with central openings, no matter how small.

HISTORY

Meckel in 1812 attributed the first recorded case of intestinal atresia to Benringer in 1673; this patient had a total atresia of the colon. A case of total atresia of the terminal ileum was reported in 1684 by Goeller. The first successfully treated patient was one with ileal atresia reported by Fockens in 1911 [7].

INCIDENCE

The incidence of intestinal atresia varies from 1 in 1500 [7] to 1 in 20,000 [9,18,27]. Atresia of the colon comprises less than 10 per cent of the cases of intestinal atresia; about 10 per cent of all atresias are multiple [6,7,18,24].

ETIOLOGY

One commonly accepted theory is that intestinal atresia is due to a defect in normal intestinal development. Prior to the fifth week of fetal life the intestine has a lumen which is lined with epithelium. This epithelium proliferates during the sixth and seventh weeks so that the lumen becomes blocked by epithelial overgrowth. Vacuolation of this solid plug of cells and coalescence of the vacuoles leads to re-establishment of the lumen. An arrest or imperfection of the recanalization process is believed to be the cause of membranous and cordlike atresias. Partial recanalization is believed to account for stenosis. The process of vacuolation and recanalization is typically completed by the twelfth week.

Most authors agree that this is probably the process which leads to duodenal atresia. A developmental etiology is supported by the fact that other developmental anomalies (e.g., mongolism) are more common in infants with duodenal atresia than with atresia at any other level [16,19–21,26]. The Farber test is probably most reliable in duodenal atresia [8].

In a study of eighty-nine human embryos Lynn has shown that, while epithelial plugging and vacuolation *can* occur in both the large and the small bowel, it does not occur *regularly* in any area. It appears most frequently in the duodenal area. It has been widely assumed that plugging and recanalization was a constant phenomenon, yet in Lynn's study it actually occurred in only one third of the embryos [18].

Many authors believe that the recanalization theory is not an adequate explanation for atresia of the intestine below the ligament of Treitz. The recanalization theory cannot explain the defects of bowel substance or the mesenteric defects so commonly noted in the lower atresias [1,4,14,17,19,22].

In some cases squamous epithelial cells have been found in the lumen of the intestine below

TABLE I
TYPES OF ATRESIA AND PERCENTAGE OF SURVIVAL

Atresias*	No. of Cases	No. of Survivors	Survival (%)
Duodenal	28	17	61
Jejunal	26	7	27
Ileal	33	20	60
Colon	4	3	75
Total	91	47	52

* Four patients with duodenal atresia, ten with jejunal atresia and one with ileal atresia were not treated definitively or had theoretically uncorrectable lesions. (See text.)

TABLE II
COMPARISON OF MORTALITY RATES IN ATRESIA

Types of Atresia and Method*	No. Cases	No. of Survivals	Mortality (%)
Jejunal†			
Resected	15 (12)	7	42
Exteriorized	3 (1)	0	100
Left in place	8 (3)	0	100
Total	26		
Ileal†			
Resected	14	12	14
Exteriorized	10	4	60
Left in place	8	4	50
Total	33		
Colon			
Resected	3	2	33
Exteriorized	1	1	0

* All cases of duodenal atresia were treated by lateral anastomosis without resection or direct attack on the atretic segment.

† Ten of the twenty-six jejunal cases and one of the thirty-three ileal cases had such extensive atresia that insufficient bowel remained to support life. Two of these were exteriorized, two were resected and the remaining seven were left in place as hopeless. The mortality in the jejunal group is calculated for the cases with sufficient intestine to support life if operative correction had been successful (sixteen jejunal atresia cases, thirty-two ileal atresia cases).

a complete atresia [*8*]. These squamous cells must be swallowed in order to reach the lumen at that level. However, there are no squamous epithelial cells of this character present on the skin or in the amniotic fluid until after the solid stage of intestinal development has passed. If atresia were due to failure of the solid intestine to recanalize, that chronologic sequence would preclude the presence of epithelial squamae below the level of the atresia [*21*].

The liver does not begin excretory function until midway through fetal life, so that the presence of bile in the meconium below an atretic area suggests that the obstruction occurred after bile flow was established [*4*].

Intestinal atresia may be a lesion that is produced by bowel injury at a later stage than the seventh to twelfth week. It has been noted that bowel deprived of its blood supply undergoes a process of shortening and constriction, with eventual replacement by a fibrous band [*23*]. Devascularized sterile segments of intestine left free in the peritoneal cavity undergo autolysis and are converted into fibrous bands [*15*].

Vascular accidents have been postulated as the cause of the lower atresias. Suggested causes for this devascularization include thrombosis of one of the arcuate arteries, intrauterine intussusception with thrombosis of the intestinal vessels and sterile gangrene, incarceration of the physiologic antenatal umbilical hernia and various other forms of vascular insult, e.g., torsion or kinking [*1,4,17–19,21, 22,26*].

Inadequate vascular supply may be related to the relatively high incidence of gangrene and perforation of the bowel in cases of atresia. In this series one patient with duodenal atresia, seven with jejunal atresia and fourteen with ileal atresia had meconium peritonitis, gangrene, perforation or necrotic bowel at the time of surgery. (The patients with these complications were of the same average age as the others who did not have these problems, so that perforation, etc., cannot be related to delay in operative intervention.)

Bernstein et al. suggest extravasation of meconium to the submucosal or even to the free peritoneal levels with formation of meconium granulomas, scarring and extrinsic compression to eventual amputation as an etiologic process [*4*]. They suspect a relationship of fibrocystic disease of the pancreas and meconium ileus to these phenomena.

In this series fibrocystic disease was demonstrated in five patients with jejunal atresia. Of these, three had meconium peritonitis at surgery. One case of ileal atresia had fibrocystic disease. None was found in the cases of duodenal or colonic atresia. In patients with fibrocystic disease or atresia, certain elements

may be lacking from the meconium, but its gross appearance is often impossible to distinguish from that of normal meconium.

It has been possible to produce lesions grossly like intestinal atresia in the dog by ligation of the intestinal vessels of the puppy *in utero*. This technic presents considerable technical difficulties, but has been successfully achieved in enough cases to demonstrate the point [*1,17*].

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Some surgeons have assumed that the enormous dilatation of the proximal segment, and its subsequent failure to develop adequate peristaltic activity, were due to a deficiency of myenteric ganglia and nerve cells. Careful studies of resected and autopsy specimens have shown that there is no anatomic deficiency of nerve cells or of musculature in the bowel proximal to an atretic segment. Animal experiments have shown that greatly dilated bowel proximal to an obstruction has a very low degree of efficiency in transmitting fluids, even though some muscular contractions are present [*21*].

The great increase in survivals when the dilated proximal segment has been resected is due to the fact that the overly stretched bowel cannot deliver an effective peristaltic rush against the resistance of the tiny edematous stoma. The remarkable decrease in the size of the lumen due to edema in an infant, compared to the much smaller influence of edema in an adult anastomosis, has been well shown [*1,3,5,26*].

The close association of hydramnios with congenital anomalies, and in particular with anomalies of deglutition or with intestinal obstruction, has been generally accepted [*2,16, 20,25*]. Twenty-seven per cent of infants born of pregnancies complicated by hydramnios had congenital anomalies. The correlation of the level of intestinal obstruction and degree of hydramnios has been impressive [*2,16,20*]. Twenty-eight per cent of our cases of duodenal atresia occurred in pregnancies complicated by hydramnios, compared to 8 per cent of the cases of jejunal atresia, 4 per cent of the cases of ileal atresia and none of the cases of colon atresia.

The normal circulation of amniotic fluid through the fetal gut is so large in amount that it cannot all be absorbed in the newborn intestinal tract. The question of whether or not some of the excess amniotic fluid comes from the secretions of the upper intestinal tract of the infant remains unanswered. In cases of high small bowel atresia, the amniotic fluid tends to be darker green in color, presumably due to the bile regurgitated by the infant. There is some evidence that the infant with atresia does not continue to have bowel movements *in utero* [*4*]. The higher intestinal obstructions apparently have a greater degree of hydramnios than the lower obstructions, since there is earlier and more persistent regurgitation *in utero*.

Because of the large volume of fluid in the stomach of newborn infants delivered of mothers with hydramnios, it has been suggested that the newborn infant's stomach should routinely be emptied by the passage of a small catheter. When this maneuver is applied, the hazard of neonatal vomiting and aspiration is reduced. Even more important, significant congenital anomalies of the upper intestinal tract are diagnosed earlier.

Failure of the catheter to enter the stomach will reveal esophageal atresia. If the volume of gastric content recovered is in excess of 35 to 50 cc., upper gastrointestinal obstruction should be strongly suspected. A supine roentgenogram of the abdomen within a few hours of birth will give a valuable estimate of the gas pattern [*20*]. In the normal infant the swallowed air has reached the lower small bowel or colon by the sixth hour after birth and will reach the anal area by the twenty-fourth hour after birth.

The history of neonatal vomiting is extremely important. Atresia of the duodenum above the ampulla of Vater is comparatively rare, so the vomitus in infants with atresia almost invariably contains bile. Biliary vomiting in a newborn infant should always be taken as strong presumptive evidence of intestinal obstruction. These infants regurgitate spontaneously, whether fed or not. The presence of bile-stained emesis on the infant's bed clothes should be a dramatic warning to the attending physician.

It might be expected that, if the infant had atresia of the duodenum below the level of the ampulla, the bile would all be lost by vomiting and consequently there would be no bile staining to the stools. Actually, in this series of infants with this anomaly, the stools were often as dark as normal meconium. The color of

meconium is not entirely due to its bile content [4].

In our cases of duodenal atresia, biliary vomiting was noted in all but the four cases in which the obstruction was above the ampulla. In all the other infants with atresia who had done any vomiting, there was bile in the vomitus. The lower the obstruction, the greater was the degree of distention and the less drastic the vomiting. Patients with duodenal atresia began vomiting earlier and their distention was limited to the gastric region.

One might expect that the infants with lower obstructions would be born with a greater degree of distention, and this was often the case. In some, however, the infant with low atresia tolerated feedings for several days before distention and emesis became obvious problems. In these cases the absence of meconium stools is most significant. Thus, in duodenal atresia the passage of stools coupled with prompt emesis is typical. In the lower atresia the absence of stools and a certain degree of tolerance of feedings is typical, depending on the extent of small bowel distention at birth and the level of the lesion.

Prematurity was noted in 39 per cent of our cases of duodenal atresia, 38 per cent of the cases of jejunal atresia and 27 per cent of the cases of ileal atresia. This is consistent with other reported series. The average gestational age was thirty-six weeks in this series of cases. We could not demonstrate any consistent relation of hydramnios to prematurity in this series, although there is reason to expect some correlation [*16,19,20*]. Atresia in an infant weighing less than three pounds was uniformly fatal, though we regularly attempt correction in the hope of a successful result.

The incidence of the various types of atresia had no consistent relation to birth rank or to sex in this series. This has been noted in other reports on this subject. There were no cases with a family history of atresia or stenosis in this series.

Patients with duodenal atresia tend to be treated at a later age than those with atresia in lower areas of the intestine. This is probably due to several factors: (1) babies with duodenal atresia do not appear as dangerously ill as early in life because they are less distended; (2) the emesis may not be alarming until several days have passed; (3) these infants almost always had a history of having passed meconium stools, regardless of whether the lesion was proximal or distal to the ampulla of Vater. This passage of apparently normal stools may confuse the attending physician and lead to a delay in diagnosis.

ASSOCIATED ANOMALIES

The number of associated anomalies was highest in the group with duodenal atresia, in which 60 per cent had some other anomaly. The most common anomaly encountered was Mongolism, occurring in 20 per cent of the cases. Other anomalies were seen in 11 per cent of the cases with jejunal atresia, in 12 per cent of the cases with ileal atresia and none in the four cases of colon atresia. These findings support the concept that duodenal atresia is a developmental anomaly occurring at the same time that the other disorders of growth and development occur.

EXAMINATION

Physical. One point of clinical interest was that, in many infants with small bowel obstruction, the rectal examination proved to be misleading to the unwary. Since no stools had passed the rectum and lower colon, these structures were very small in caliber. On digital examination the rectum appeared to narrow markedly or to end blindly. Several cases were referred to this hospital with a diagnosis of rectal or lower colonic stenosis or atresia, who actually had a normal rectum and colon, but had an atresia of the small intestine. Aside from this, the only physical findings were those of dehydration and obstruction. The average body temperature of infants with atresia was 36°C.

Laboratory. In this series the urine on admission frequently contained albumen and white blood cells. These urinary abnormalities are reversible once adequate hydration is established.

Roentgenograms. The value and necessity of supine films is obvious. In this series four patients were subjected to upper gastrointestinal studies with barium and four had barium enemas at this hospital. All of the barium enemas were done in cases of small bowel atresia and one upper gastrointestinal series was done in a case of jejunal atresia.

One case was diagnosed by roentgenogram as having a duodenal obstruction, but at surgery the obstruction was not considered to be complete and accordingly the abdomen was

closed without a bypassing anastomosis. The infant died without further exploration and at autopsy the duodenal atresia was demonstrated. This error has been reported from other centers also. Feggetter commented upon two similar cases and stated that, whenever the signs and symptoms together with the x-ray studies indicate that a duodenal obstruction is present, it is better to do a lateral anastomosis even though the obstruction may not be impressive at the time of laparotomy [9]. Parenthetically, the classic "double bubble" of duodenal atresia has not always been found in our cases. It is a valuable sign when it can be demonstrated, but it is not always seen in cases of duodenal obstruction.

Barium studies are not usually needed to establish the necessity for operative intervention. The time lost and the necessary manipulations of the infant are not advantageous, once the diagnosis of obstruction has been made on clinical grounds and confirmed by ordinary supine roentgenogram of the abdomen. Early correction of fluid and electrolyte imbalances and prompt surgical intervention are better management than prolonged x-ray studies. One infant was transferred to this hospital after an attempted barium enema done elsewhere had perforated the colon and filled the peritoneal cavity with the barium material.

OPERATIVE MANAGEMENT

With the improvements in anesthesia, supportive fluid therapy and antibiotics, the major problem of restoring intestinal continuity and function has been made somewhat easier. It is essential that function be restored as promptly as possible.

In our series, this objective was best attained by adherence to certain principles: (1) adequate decompression of the intestinal tract before and after the operative correction; (2) although no one type of anastomosis had any clearly demonstrable superiority over any other in this group of cases, (3) it can be clearly shown that *resection* of the dilated proximal segment of the atretic bowel is associated with a markedly better survival rate than that obtained by any technic in which the dilated bowel is left in place; (4) a thorough exploration for multiple areas of atresia is essential.

Any infant who can tolerate operative correction of an atresia can tolerate exploration of the remaining bowel for other areas of obstruction. The incidence of multiple atresia is fairly high (10 per cent).

Incomplete exploration was one of the causes of failure in one of our cases and this error has been reported in other series [*12,19,28*]. The bowel distal to the anastomosis should be distended with air or fluid to determine the fact of its patency down to the level of the peritoneal reflection on the colon. The adequacy of the lumen below that point should have been determined by rectal examination prior to exploration. The distention of the bowel distal to the obstruction has the advantage of loosening any plugs of meconium that may be present and of preparing the bowel for the passage of material following the restoration of continuity.

We believe that continuous decompression of the bowel in the postoperative period contributed materially to the good results obtained. This added protection to the suture line was particularly important if the dilated segment proximal to the atresia was not resected. Decompression had its greatest value in cases in which lateral anastomosis had been done, as in duodenal atresias, and in cases of extensive atresia in which resection was not undertaken in an effort to conserve as much bowel as possible.

We have used ordinary nasogastric suction with a fine plastic or rubber tube, but have come to prefer catheter gastrostomy. The use of a catheter enterostomy just proximal to or across the anastomotic line has been favorably reported elsewhere, though our staff have not used it very often [*11,19*].

The use of a catheter gastrostomy has definite advantages over an indwelling nasogastric tube. The latter tends to induce gagging and aspiration, is often unreliable in function and requires constant nursing attention to maintain efficient suction and decompression. In the small food and air passages of these infants, the irritation of an indwelling tube can become serious, with local infection, ulceration and subsequent scarring (see the section on jejunal atresia).

It has been a common experience, both at this hospital and elsewhere, to find that a patent anastomosis does not function effectively when the dilated proximal segment has been left in place. Nixon, for example, quotes fifteen cases performed with primary anastomosis, without resection of the dilated segment, with five survivals and another fifteen cases with resec-

tion of the dilated segment, with ten survivals [21]. Benson, Swenson and Clatworthy are also strong advocates of resection wherever feasible [3,26].

DUODENAL ATRESIA

In this series there were twenty-eight cases of duodenal atresia, but four of these (14 per cent) were not treated definitively. Two of these infants were in critical condition on admission and died within forty-eight hours. One three pound infant had an esophageal atresia and tracheoesophageal fistula in addition to the duodenal atresia. Both conditions were correctly diagnosed and the esophageal lesion was corrected first. The infant died on the first postoperative day and was found, at autopsy, to have congenital heart disease and bilateral polycystic kidneys.

The fourth case is something of a puzzle to us. The baby was referred to this hospital from an isolated community 200 miles away, having had little or no supportive treatment in the three weeks since birth. In spite of the fact that we now know nothing had passed the duodenum, and that all of the feedings had apparently been vomited, the infant was in a surprisingly good hydrational and nutritional state. At exploration it was believed that there was a lumen in the duodenum and accordingly no bypassing anastomosis was performed. The infant died on the ninth postoperative day of aspiration pneumonia. At autopsy the presence of the duodenal atresia was demonstrated.

A total of twenty-four patients were treated definitively, of whom seven ultimately died (29 per cent). With reference to the earlier comment about the insidious nature of this anomaly, the average age of the cases of duodenal atresia at the time of admission was 4.6 days. In all other forms of intestinal atresia the average age at admission was 2.5 days. We had four infants with duodenal atresia who were more than eight days old at the time of admission, including the three week old infant just mentioned. None of the patients with atresia lower in the intestinal tract were more than six days of age at the time of admission.

The pregnancy was complicated by known hydramnios in eight of the twenty-eight cases (28 per cent) and the infants were premature in eleven cases (39 per cent). Sixteen infants were girls and twelve were boys. The birth weight of the infants fell within the normal range in most of the cases, though five of them weighed less than four pounds.

Biliary vomiting was reported in twenty-three of the twenty-eight cases (82 per cent). In four cases the lesion was above the ampulla and the vomitus did not contain bile and in one case there was no history of vomiting. Seventeen of the twenty-eight cases (60 per cent) had passed apparently normal meconium stools. One infant had been a problem in resuscitation at birth.

Less than one fourth of the patients showed evidence of distention or visible peristalsis. The abdomen was silent in about one third of the infants.

We have the clinical impression that the smaller babies may have a better survival rate. Twenty-two of the babies (78 per cent) had a body weight of less than 6 pounds at the time of definitive surgery and all but two of the seventeen survivors were in this group.

Laboratory Work. At the time of admission the findings on urinalysis in the majority of cases were those of dehydration. Two infants had hemoglobin values of less than 10 gm. per cent on admission, although, in this age range, anemia is uncommon. The normal hemoglobin range in this age group is 16 to 17 gm. per cent. One half of the infants had hemoglobin values in excess of 18 gm. per cent. This is simply an expression of the dehydration added to the physiologic polycythemia at this age. We obtained some blood chemistry values on about one third of the infants, usually serum chloride and carbon dioxide levels. These values were not of major diagnostic significance.

Roentgenograms were routinely obtained; the supine film being adequate to make the diagnosis in most cases. Barium studies of the upper or lower bowel were done here or elsewhere in five instances. The preoperative x-ray diagnosis was uniformly correct in this group of cases. The single error in clinical diagnosis has been previously described.

Preoperative Preparation. Upon admission about one half of the infants were placed in incubators with external heat and supplemental oxygen. In recent years most of the infants have been managed in this way.

In all but three cases a tube with nasogastric suction was employed from the time of admission. Blood and/or plasma transfusions were given to three infants in this series. Antibiotics

were given in about one half of the cases, usually for pulmonary complications, and supplemental vitamin K was given in six cases. Hydration otherwise was routine.

Operative Management. General anesthesia was used in all but one and a vertical abdominal incision was used in all but three of the patients. Needless to say, no direct attack upon the atretic segment was undertaken.

Meconium peritonitis was seen in one case in this group with no detectable perforation of the bowel. This complication was far more common in the infants with lower atresia in which it was usually due to gangrene with perforation.

Five cases (18 per cent) were treated by gastroenterostomy, chiefly in the earliest years of this study. There were two deaths in this group, one due to aspiration on the seventh postoperative day and the other from bronchopneumonia on the fortieth postoperative day.

Seven patients (25 per cent) were treated by *retrocolic* isoperistaltic duodenojejunostomy, with one death on the third postoperative day. This was in a mongoloid infant who was found to have bled into the lung, cerebellum and gastrointestinal tract with an associated annular pancreas in addition to the atresia. One case was reoperated upon for angulation at the site of the anastomosis and had a reanastomosis without further difficulty. Six of these cases had a two layer anastomosis and one case had a one layer anastomosis.

Six other infants (21 per cent) were treated by *antecolic* duodenojejunostomy with four survivors. One of the deaths occurred on the second postoperative day following successful resuscitation of a cardiac arrest during surgery. There were no surgical complications in the survivors. Three of the six cases had a one-layer anastomosis.

Six other patients (21 per cent) were treated by duodenojejunostomy, but the position of the colon was either not stated, or the colon was not normally placed. There were two deaths. One death occurred in a patient with three separate diaphragms in the bowel, in addition to the atresia. The patient did not do well, and the diaphragms were found at a second operation. Death occurred from bronchopneumonia. A second death occurred on the seventh postoperative day of aspiration pneumonia. Three of the cases had a one layer anastomosis.

In this series there did not appear to be any difference in the survival rate, or the immediate complication rate, of gastrojejunostomy as compared to duodenojejunostomy [9]. On the basis of adult experience, it would seen desirable to avoid a gastrojejunostomy and prevent any future difficulties with ulceration. There were no anastomotic leaks with either a one layer or a two layer anastomosis. One case had prolonged closure of the stoma by edema, following a two layer anastomosis, but eventually the stoma opened up.

The anastomosis was accomplished with one layer of sutures in twelve cases (50 per cent) and two layers in twelve cases. The one layer anastomoses were all done with nonabsorbable sutures. One case had a two layer anastomosis done entirely with absorbable sutures, while in all of the remaining cases the surgeon used nonabsorbable seromuscular sutures and absorbable mucosal sutures. The abdominal closure was done entirely with nonabsorbable sutures in fourteen cases, with all absorbable sutures in one and mixed in the remainder. There were no wound disruptions and only one wound infection. On the basis of this experience, we cannot claim a distinct advantage for any type of lateral anastomosis over any other for duodenal atresia.

Seventeen patients of the twenty-four subjected to definitive surgery left the hospital alive (71 per cent) and have been followed for varying periods.

Of the eleven premature infants in this series, six lived (55 per cent) and five died. Of the seventeen infants of normal gestational age, eleven lived (65 per cent) and six died. It would appear that prematurity does carry an added risk in this, as in other major congenital anomalies, but it was not the major cause of death in this series [12,19,24].

JEJUNAL ATRESIAS

There were twenty-six cases of "jejunal" atresia. We have included under "jejunal" atresia ten patients who had very extensive atresia of the small bowel extending to the terminal ileum or to the colon, leaving insufficient bowel to maintain life even after a functioning stoma (e.g., duodenocecostomy) had been created. A transit time, mouth to anus, of less than three minutes has been noted in such a case [19]. Of the remaining sixteen patients in whom correction was theoretically feasible, there were seven survivals (43 per cent).

Age and Sex. The infants with atresia of the jejunum and ileum were much younger on the average than those with duodenal atresia. The average age at admission was 2.3 days and no case was more than five days old on admission. The cases were equally divided by sex, thirteen of each.

Pregnancy and Prematurity. In the cases of jejunal atresia, the incidence of delivery by cesarean section was about the same as it was in atresias at other levels (8 per cent). The pregnancy was known to be complicated by hydramnios in only two of the twenty-six cases (8 per cent) of jejunal atresia. Ten of the twenty-six infants were premature (38 per cent); one of the infants weighed less than 3 pounds. The babies with jejunal atresia tended to be slightly heavier (average 6 ounces) than those with duodenal atresia, but no clinical significance can be attached to this fact.

Three of the twenty-six infants had had no known vomiting prior to admission, but the vomitus in all of the remainder was bile stained. Only three of the infants with jejunal atresia had passed stools. These stools were believed to be normal meconium in two infants; in the other, a female, stool on the day of admission was bloody. At operation she was found to have a volvulus of the small bowel with a failure of rotation in addition to the atresia. The bowel was gangrenous and was resected. She survived that procedure but required a second laparotomy one week later for obstruction of the stoma. She developed an overwhelming cellulitis and gangrenous infection starting at the nostril, possibly related to the presence of the nasogastric suction tube. She died of overwhelming necrotizing sepsis of the face and head ("midline gangrene").

Three of the infants with jejunal atresia were twins, and in all instances the other twin was normal.

Examination. Distention and tympany were noted in nineteen of the twenty-six cases (73 per cent), with visible peristalsis present in seven cases (27 per cent). The others did not show these findings usually because so much of the bowel was atretic. The abdomen was silent in nine of the patients (34 per cent), seven of whom had perforated or gangrenous bowel with peritonitis at the time of admission.

The incidence of associated anomalies was very low; only three were found in the entire series.

In the cases with jejunal atresia, the survivors tended to be slightly larger babies. The average weight of the entire series was 4.6 pounds, but the average weight of the survivors was 5 pounds. This is almost exactly the reverse of the weight situation for the infants with duodenal atresia. We do not attach any particular significance to these observations.

Laboratory. Urinalysis revealed some evidence of dehydration in a somewhat smaller proportion of the cases of jejunal atresia (and ileal atresia) compared to those with duodenal atresia. As in all the other forms of atresia, the hemoglobin values on admission were high. None of the patients had a hemoglobin value of less than 12 gm. per cent on admission. These "high" values (average 17.5 gm. per cent) are the result of dehydration in addition to the physiologic polycythemia.

Roentgenograms. Supine films of the abdomen were obtained in all cases; twenty-two of them had the x-ray studies done in our hospital, and in the remainder the films taken elsewhere were satisfactory for determining the diagnosis. None of the patients had preoperative barium studies done here, though they were done postoperatively in several cases with questionable function at the stoma. The correct diagnosis was made preoperatively in all twenty-six cases, (i.e., small bowel atresia; the distinction between jejunal and ileal atresia was made at operation).

Preoperative Preparation. Eight of the infants were placed in incubators and received supplemental oxygen. Twenty-three of the twenty-six patients had nasogastric suction instituted preoperatively. The state of hydration was brought to normal by parenteral fluids whenever needed. During and after the operative procedure, transfusions were given to five of these infants and antibiotics to nine of them. Supplemental vitamins, especially K, were given to six patients.

Operative Management. In four of the infants (15 per cent) there were multiple areas of atresia. In seven of the twenty-six (27 per cent) the bowel was necrotic, gangrenous or perforated, with associated peritonitis. In one additional patient there were many adhesions present, the cause of which was not apparent. In three there was no hope of a successful result, so that no attempt at definitive reconstruction was made.

General anesthesia was used in all of the pa-

tients and a vertical abdominal incision in all but three infants.

The proximal atretic segment was resected in fifteen (58 per cent) of the cases, including those that were exteriorized. The proximal and distal ends were exteriorized in three, all of whom died. A bypassing lateral anastomosis with no effort to resect the atretic segment was done in five cases (19 per cent). In some of the extensively atretic cases, the proximal bowel was exteriorized in the hope of eventually restoring continuity with a minimal resection, but this hope was never realized. In one particularly difficult case a temporary T-tube splint across the suture line was used, but the baby subsequently required reoperation because of an anastomotic leak.

A total of sixteen side to side or lateral anastomoses (61 per cent) were performed, including those infants treated by exteriorization. This group includes some of the extensive cases previously noted in which eventual success was impossible. A total of seven end to end procedures (27 per cent) were performed as the primary definitive therapy. None of the patients were treated by end to side or side to end anastomoses, though these have found some favor elsewhere.

A proximal enterostomy tube was used in three cases with only indifferent success. In eight of the cases (including some of the cases too extensively involved for any definitive surgery) the distal bowel segment was *not* distended by the operator. In all of the remainder the distal loop was distended and its patency demonstrated, if a primary anastomosis was done.

In all types of atresia of the small bowel below the ligament of Treitz, there was a higher survival rate in those patients in whom the dilated proximal segment was resected.

Of the thirteen infants treated by side to side anastomosis with five survivors (38 per cent), all but one of the survivors had resection of the dilated proximal bowel. In this one case a second procedure was done because the stoma failed to open up and at the second procedure the bowel *was* resected and reanastomosed with complete recovery. There were no anastomotic leaks in the patients treated by resection.

Of the eight infants treated by side to side anastomosis who died, four did not have resection of the dilated proximal bowel. Of these, one had a leak at the anastomotic site and expired of peritonitis with miliary abscesses. One premature infant died of bronchopneumonia the first day after surgery; the anastomosis was intact. One died on the twenty-eighth postoperative day of bronchopneumonia and partial small bowel obstruction due to adhesions. Another had a second operation on the fifth postoperative day because the stoma did not function, and died fourteen days after the second operation of respiratory infection.

In the group of sixteen "feasible" cases there were seven infants (44 per cent) treated by end to end anastomosis with two survivors, both of whom had resection of the proximal dilated end. Both of these had to have a second procedure, however. In one a patent anastomosis was found with dilated bowel proximal to the stoma. Re-resection and a side to side anastomosis was done with recovery. In the second case, the stoma was patent but was narrowed by edema. A side to side anastomosis around the narrowed area was done with recovery.

The five deaths that occurred in cases with an end to end anastomosis were as follows: two of them did not have a resection of the dilated proximal segment and both apparently died of peritonitis. One patient had a resection of the proximal dilated segment and end to end anastomosis which functioned adequately, but the patient died on the tenth postoperative day of thrombosis of the pulmonary veins. One died of peritonitis after an anastomotic leak and one died of overwhelming "midline" sepsis and gangrene, starting at the nose, possibly related to the nasogastric tube.

In the cases of jejunal atresia, then, there were a total of sixteen patients in whom operative correction was theoretically feasible. Twelve of these had a resection of the dilated proximal bowel with seven survivals. None of the deaths in the cases of resection could be attributed to leakage or failure of function of the anastomosis.

The anastomosis was performed entirely with nonabsorbable sutures in nine cases and with mixed suture material in the remainder. A one layer anastomosis was carried out in eleven cases and a two layer anastomosis in nine cases.

Antibiotics were instilled into the peritoneal cavity in only one case, largely because meconium peritonitis is a sterile process in almost every instance.

Wound closure was accomplished entirely

with nonabsorbable sutures in fifteen cases and mixed suture material in eleven cases. There were no instances of wound disruption and only one wound infection. There were three anastomotic leaks, including the one case in which a T-tube splint was used. This case resulted in a fistula and the patient was reoperated upon with only partial success. The infant eventually died of peritonitis although the bowel leak had been controlled.

Results. We attribute fifteen of the deaths to the atresia itself and/or the complications of the treatment of that anomaly. Four of the deaths we attribute to disease other than the major anomaly, chiefly respiratory infections, complicated by fibrocystic disease of the pancreas.

Five of the patients had to have a second operation with revision or reconstruction of the stoma and four required a further operation later.

A total of seven infants with "jejunal" atresia left the hospital alive (27 per cent). Of these, two were premature infants and five were normal term infants. Of those who died of any cause, eight were premature infants and eleven were normal term infants.

ILEAL ATRESIA

There were thirty-three cases of ileal atresia. These infants, like those with jejunal atresia, were much younger at the time of definitive treatment than those with duodenal atresia. They averaged 2.7 days of age and none was more than six days old at the time of treatment. There were fifteen boys and eighteen girls. Two of them had been born by cesarean section, but in only one case was the pregnancy known to be complicated by hydramnios. Nine of the thirty-three infants (27 per cent) were premature (versus 39 per cent with duodenal atresia and 38 per cent with jejunal atresia). Their average birth weight was 5.8 pounds and one of them weighed less than 3 pounds at birth.

Two of the infants had no history of vomiting, but the remaining thirty-one had all vomited bile-stained material. Only five of the patients (15 per cent) had a history of having passed meconium stools. In four of these the "Farber" test was applied and was negative [8]. Three of the infants were twins and in all instances the other twin was normal.

Examination. The abdomen was distended and tympanitic in twenty-five of the thirty-three cases (76 per cent) and peristalsis was visible in eight. The abdomen was silent in seven cases and the presence of peristalsis not definitely recorded in four others. There was a total of fourteen patients (42 per cent) who proved to have peritonitis due to gangrene with perforation at laparotomy. Two of the thirty-three infants had congenital heart disease in addition to the atresia. The temperature on admission averaged 36.3°C.

The average admission weight of the entire series was 5.6 pounds and the average weight of the survivors was 5.7 pounds, so that no distinct advantage can be seen for either the larger or the smaller babies.

Laboratory. The only common variation from the normal on routine urinalyses was the evidence of dehydration. The hemoglobin values reflected the factors noted earlier—the average was 16.5 gm. per cent. Although other studies, such as carbon dioxide or chloride determinations, were carried out occasionally, there was no consistent alteration in the values obtained.

Roentgenograms. Ordinary supine films of the abdomen were obtained in all cases; in five cases the films taken outside the hospital made the diagnosis clear.

A barium enema was given in one case; no other barium studies were undertaken. The x-ray and clinical diagnoses were uniformly correct in recognizing the obstruction.

Preoperative Preparation. All of the infants had nasogastric suction instituted preoperatively. Eight of them were kept in incubators with supplemental oxygen preoperatively. Fourteen of the infants received antibiotics during the pre- and postoperative periods and six of them received blood or plasma transfusions during or after the procedure.

Operative Management. Four of the infants proved to have multiple atresias and fourteen of them had other gastrointestinal complications, such as perforation with peritonitis or Meckel's diverticulum. One patient had to be operated upon for pyloric stenosis sixteen days after correction of the intestinal atresia. We regret that a detailed study of the pylorus had not been made at the time the atresia was corrected.

Local anesthesia was used in one very small premature infant, but general anesthesia was

used in all the others. A transverse incision was used in one case, but a vertical incision was used in all of the others.

In the entire series, only one infant had such extensive atresia and peritonitis that a definitive procedure was hopeless and nothing was done.

In ten cases (30 per cent) some form of exteriorization was done. Of these 10 patients, five died within a few days of surgery from the complications of established peritonitis, bronchopneumonia or other sepsis (one possibly starting from a cut-down in pre-antibiotic days). One other had a subsequent procedure attempting to restore continuity, but the infant died following the second procedure.

Four of the ten infants treated initially by exteriorization eventually survived, though all had a subsequent procedure to restore continuity. In two, the bowel was resected and continuity restored, and in two patients a lateral anastomosis was performed without resection.

Thirteen infants (39 per cent) were treated by side to side anastomosis. Six of these thirteen had some resection of the atretic area and five of them survived. The one death was due to cardiac arrest, restarted on the table, but the heart stopped again on the ward the next day.

The remaining seven cases (21 per cent) with lateral anastomoses, but *without* resection of any bowel, resulted in three survivors. The four deaths were due to volvulus in one case, possible overhydration in one, and to peritonitis from perforation of the bowel in two cases.

Seven infants (21 per cent) were treated by end to end anastomosis and only one died. This infant had an extensive atretic area resected, but expired on the sixth postoperative day without ever opening up the stoma. Autopsy permission could not be obtained. Of the six survivors, five had resections of varying lengths of the affected bowel.

Two infants (six per cent) were treated by end to side anastomosis after resection of involved bowel. Both survived, including the infant who subsequently developed pyloric stenosis.

Of all patients with ileal atresia, sixteen were resected and anastomosed, and only two died. Seventeen were not resected, and only six of them survived. These figures are very impressive to us.

The mortality rate in jejunal atresias with resection of the dilated proximal segment was 42 per cent, in comparison to 100 per cent in those cases in which the dilated segment was left in place. In the ileal group, this difference was greater, with a mortality of 14 per cent of those having a resection as compared to 50 per cent in those in whom the dilated segment was left in place.

In the group having exteriorization, the mortality is the highest. This group had this very high mortality for two reasons: First, these infants were largely treated in the earliest years of the period covered by this study, the late 1930's and early 1940's. Secondly, there was a higher incidence of perforation and established peritonitis at the time of surgery in the group treated by exteriorization.

The use of exteriorization procedures in cases with perforation and peritonitis is debatable, but the results with this procedure should not be taken as a condemnation of the *method*. Exteriorization was not regularly used on cases in which a primary anastomosis was feasible.

The anastomosis was accomplished entirely with absorbable sutures in only one case; in nine cases with only nonabsorbable sutures and in the remainder (twenty-two cases) the sutures were mixed.

The anastomosis was performed with one layer of sutures in seven cases, and with two layers in eleven cases. Closure of the abdomen was carried out entirely with absorbable sutures in only one case; in the remainder nonabsorbable sutures were used wholly or partially.

There were no wound disruptions and only three wound infections. There was one anastomotic leak. Two patients required subsequent reanastomosis and three were subjected to other procedures for problems related to the atresia and its attempted correction.

Results. Twenty of the thirty-three infants (60 per cent) left the hospital alive. Of the nine premature babies, five lived (55 per cent) and four did not. Of the twenty-four infants of normal gestational age, fifteen (62 per cent) left the hospital alive and nine died.

COLONIC ATRESIA

We had only four cases of atresia of the colon; three in the transverse colon and one at the hepatic flexure [*10,13*]. Two of the infants were one day old and two were two days old at admission. There were two of each sex. Three

weighed over 7 pounds on admission, the other weighed 5½ pounds. Three had a history of biliary vomiting, but one had not vomited at all. None had passed any stools. All were found to be distended and tympanitic on admission, but only two had audible peristalsis. None had evidence of perforation or peritonitis. Their other physical findings were not remarkably different from the infants with lower small bowel atresia. They had the same evidence of mild dehydration reflected in the urine examination and blood counts.

The roentgenographic studies did not include a barium enema in any of the four cases. The location of the atresia in the colon was suspected in three cases on the supine film alone, and not suspected in the fourth case. None of the infants was given oxygen or placed in the incubator preoperatively. Three had nasogastric suction begun preoperatively but one did not. All were operated upon under general anesthesia and through vertical incisions. The atresia was resected in two, bypassed in one and exteriorized in one. A subsequent procedure to close the colostomy was done some months later.

The only wound dehiscence in this entire series of cases occurred in an infant with a complete atresia of the transverse colon. A side to side ileosigmoidostomy was performed using two layers of sutures. The wound disrupted on the twelfth postoperative day and an anastomotic leak was discovered, or appeared, then. An ileostomy was performed with the sigmoid brought out as a mucous fistula. The infant died of sepsis and liver failure on the eighth day after this procedure. This was the only death in the four cases of colonic atresia.

Long Term Followup. We have been able to achieve about an 80 per cent follow up on these cases. We know of only two patients who required any operation for intestinal disease after discharge from the hospital. One infant with colon atresia was operated upon for intestinal obstruction due to adhesions at two and one-half years of age. One patient with jejunal atresia was operated upon elsewhere for what was believed to be appendicitis. The appendix was not inflamed but there was evidence of mesenteric adenitis.

One infant with jejunal atresia is known to have died of cystic fibrosis of the pancreas one year after discharge. One other child died of some obscure infection three years after discharge and another died of congenital heart disease four years after discharge. We are now following one case with a persistent anemia that we suspect may be related to a "blind pouch" following a lateral anastomosis. The anemia is not macrocytic and there is no disturbance of gastrointestinal function.

All of the other patients we have been able to follow have had normal gastrointestinal function.

SUMMARY

1. Biliary emesis in the newborn is pathognomonic of intestinal obstruction.

2. Duodenal atresia has the highest incidence of associated anomalies. Duodenal atresia is probably a developmental defect in recanalization. Atresia below Treitz' ligament may be an "acquired" lesion developing after the twelfth week of fetal life.

3. Infants with duodenal atresia commonly pass meconium stools; those with lower atresias do not. The "Farber" test is probably most reliable in duodenal atresia, much less so in more distal lesions.

4. Marked abdominal distention regularly occurs with lower atresias, uncommonly with duodenal atresia.

5. There is no evidence of an anatomic defect of the myenteric plexus in the dilated bowel proximal to an atretic segment.

6. The unused rectum may be mistakenly diagnosed as stenotic or atretic in patients with atresia of the small bowel.

7. Proximal decompression is essential to successful management of atresia. Catheter gastrostomy is one efficient method of decompression.

8. We are unable to demonstrate a clear superiority for any type of anastomosis: one versus two layer; end to end versus side to side in the management of atresia (exclusive of duodenal atresia).

9. Clearly, there is an enormous advantage to resection of the dilated proximal segment wherever it is technically feasible. Effective peristalsis is essential to overcome the temporary resistance of the edematous stoma and dilated overstretched bowel cannot deliver an effective peristaltic rush.

10. Anastomotic leaks are rare when the proximal dilated segment is resected, regardless of the type of anastomosis used.

11. Malfunction of a demonstrably patent

stoma is due to edema and ineffective peristalsis. Angulation or kinking are relatively minor factors.

12. Exteriorization procedures have been largely unsuccessful because they were used when primary anastomosis was not feasible. The bad results do not necessarily condemn the method.

13. An infant able to withstand operative correction of a known atresia should invariably have a complete exploration for other areas of atresia.

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DISCUSSION

Edwin G. Clausen (Oakland, Calif.) It is unfortunate that Dr. Bergin did not have time to give the details found in his paper and which should be read by all later. My discussion will pertain to jejunal and ileal atresias since the management of duodenal and colonic atresias has been fairly well established. I deviate only to mention that one must be aware of duodenal atresia associated with malrotation. We have had three cases in which these anomalies coexisted and in which the duodenal atresia was unnoticed at the primary operation for malrotation. Similar cases have been reported and must be recognized when air in the intestinal tract does not descend into the jejunum.

Although there are now many reports concerning the management of ileal and jejunal atresias, none of these are extensive and the personal experience of any one surgeon is limited. We have had twenty-five cases of small bowel atresias in the past fifteen years at the Children's Hospital of the East Bay. Of this group of twenty-five, six had lesions incompatible with life. We have had eight survivors. I have studied these cases in detail but there are many questions still unanswered in my mind. In six instances reoperation was necessary because of a nonfunctioning patent stoma. The type of anastomosis did not seem to be a factor although of course a number of cases are statistically insignificant.

We now recognize that at least some of the

atresias may be acquired under varying circumstances. It is obvious from our study that the majority of cases resulted from some intra-abdominal catastrophe. Those patients in whom bowel function was normal before atresia developed may be the ones whose intestinal tract functions so well postoperatively. In some instances distal loops appear small but functional while others are completely collapsed and matted by adhesions. Dr. Bergin and Dr. Pollock's best results were with primary end to end anastomosis advocated by several authors, yet one cannot help but believe that these were done on the most favorable patients. I have had a personal communication with Dr. Gross who still believes that the exteriorization method is preferable. Several authors believe that proximal decompression is necessary. It is my belief that primary anastomosis may be preferable under ideal circumstances, but that more over-all survivals will be obtained by the average surgeon with a double barrel ileostomy. This permits irrigation of the distal loop and the secondary anastomosis can then usually be done seven to ten days later.

Resection of the proximal dilated loop must be done as shown by the cases presented. Additional aspiration of the dilated proximal bowel will hasten the return of peristalsis. The use of a gastrotomy tube to replace the nasogastric suction results in more efficacious decompression and fewer respiratory complications.

After a careful review of our cases I have come to the conclusion that the greatest yield will be attained if the following principles are followed: (1) Resection of the blind dilated proximal loop and aspiration of the dilated proximal bowel; (2) irrigation of the distal bowel to determine its patency; (3) exteriorization of both proximal and distal loops with irrigation of the distal loop and subsequent secondary anastomosis, (4) the use of a gastrotomy tube for proximal decompression.

Murray L. Johnson (Tacoma, Wash.): I wish to present a case which shows how some atresias may be produced. I think this will verify some of the statements of Drs. Bergin and Pollock.

I have operated recently on a newborn infant with jejunal atresia that nicely illustrates one possible mechanism. There was typical complete atresia of the midjejunum, with the bulbous ending of the segment completely closed off. Examination of the contents of the contracted distal segment, however, showed bile-stained green meconium, indicating prior connection, and also there was considerable amorphous yellow-green material extravasated free into the mesentery. This must have been a case of an intra-abdominal catastrophe of a previously continuous bowel, with gangrene, extravasation and spontaneous healing.

Findings here indicate that aresia can be acquired. I am, however, by no means certain that all cases are in this category.

Dean K. Crystal (Seattle, Wash.): At our Children's Hospital in Seattle we have been interested in this subject lately and alarmed enough at our mortality, so that recently we have investigated our statistics. I am somewhat comforted to see that our mortalities are about those of the essayist.

The one important lesson we seem to have learned from our series is the need for prompt recognition of trouble if these babies do not do well immediately after surgery. In the literature I have seen the statement by Dr. Swenson, of Boston, that one should wait five or six days and then reoperate on a baby if things are not going well. I think we would conclude from our recent experience that that is too long, and I should like to report on one case in which prompt intervention was helpful.

The patient was a baby who had atresia of the jejunum, and we used the precaution mentioned of injecting the distal loop with saline. It passed readily enough and we had no reason to suspect that there was any additional trouble.

Forty-eight hours later, however, the baby obviously was not doing well; and when we reoperated, we discovered that by passing a catheter into the distal loop there were two incomplete diaphragms which permitted saline to go through, but which evidently were inconsistent with satisfactory bowel function. With resection of the incomplete diaphragms, which lay distally, the baby did well. While we have not a large enough series to document this, we think that prompt reintervention is almost as important as prompt primary intervention.

Werner E. Zeller (Portland, Ore.): I wish to stress again a point that Dr. Crystal just brought out, namely, the need for prompt reintervention on a patient who is not doing well.

I would like to cite one case of a newborn infant who had been operated upon because of a defect in the abdominal wall about two inches below the umbilicus. The defect extended through the entire wall and skin through which a loop of intestine protruded.

The surgeon who operated upon this child replaced the bowel within the abdomen and closed the abdominal wall defect. The patient did poorly and five days later had a sudden pneumoperitoneum. The infant was reoperated upon and a perforation was noted in the small bowel. The perforation was repaired and the abdomen closed. The child failed to put out any stool or meconium for the next four days and again a pneumoperitoneum resulted.

At this time the child was transferred to Doernbecher Hospital where I happened to see the infant.

At reoperation atresia of the terminal ileum was noted. Although there was continuity of the bowel, there was a web or some obstruction which prevented fluid from going through. The perforation at this time was down in the terminal ileum. A resection of this segment, including the area of perforation and the first portion of the cecum with an end to end anastomosis, was successful in curing this baby's obstruction.

The important thing I think is the fact that the distention in the obstructed bowel is enough to knock out the blood supply in segments, resulting in necrosis and perforation.

FREDERIC H. BENTLEY (Portland, Ore.): I intervene only to stress what Dr. Clausen has stressed already, the value in babies of a two stage resection when the judgment of the surgeon tells him that a one stage operation is too much for the baby to stand. It does not mean that every infant has to be operated upon by a two stage method. It is a matter of judgment at the time. In many infants, of course, one stage resections will do well.

At the same time the two stage resection has sometimes been given a bad name by some writers. They say, first, that it is unnecessary; and second, that after the first operation it is difficult to maintain the child in adequate fluid and salt balance in the presence of a discharging ileostomy or jejunostomy. This is no longer true under the present conditions of baby surgery in this country. If the surgeon's judgment causes him to believe that resection and anastomosis is hazardous, it is a simple matter, after excision, to bring the two ends of small gut to the surface and close the wound around them. It is better not to suture the bowel to the peritoneum or sheath. If the ends of bowel protrude half an inch or so through the skin, they stay in position very well, fixed adequately by dressings and by the catheter tied into each end. The operation is a short one.

The proximal end of intestine starts to discharge bowel contents within forty-eight hours as a rule, earlier and apparently easier than through a bowel suture line. It is my practice then to reoperate within the next twenty-four hours, when it is a simple matter to reopen the wound and complete the operation.

I have done this only once for atresia, but I have now a consecutive series of seventeen cases in which it was performed for gangrenous intussusception, all in babies or young children. Twelve of these were reported to the Western Surgical Society and since then I have had five more. Of the consecutive seventeen two stage resections in babies or young children there have been no deaths and no serious complications. I mention this not just in pride, but because a method that can command such good results in such a dangerous problem is obviously a method that justifies itself.

WILLIAM F. POLLOCK (closing): I would like to thank Dr. Clausen for his discussion and say that we have also had a case of duodenal atresia in which the x-ray appearance was classic, but the atresia was not recognized at surgery. The child was not reoperated upon and died.

There are similar cases reported in the literature, and the statement has been made that if the clinical and x-ray diagnosis of duodenal atresia seems positive, the diagnosis should be accepted and a bypassing anastomosis done even if the clinical findings are not impressive at surgery.

We have also had complications from the use of nasogastric tubes, including one death from midline gangrene, which we believe to have begun with a nasogastric tube. We are strongly in favor of catheter gastrostomy.

With regard to exteriorization, our results do not necessarily condemn this method. Dr. Benson in Detroit, Dr. Swenson in Boston and Dr. Clatworthy in Columbus have all strongly advocated resection and primary anastomosis wherever this is technically feasible. We certainly subscribe to this view. It is true that exteriorization has had a bad name for the reasons that Dr. Bentley mentioned. The fluid and electrolyte losses, particularly in very high stomas, are often lethal in these very small infants, and it does require a second and even a third stage.

We are of the persuasion that if the child does not do well following a resection and anastomosis, exteriorization may very well be a life-saving procedure. We do not condemn this method. It is simply that we have attempted resection whenever we thought it was feasible.

I should also mention the fact that hydramnios is an important precursor or premonitory sign of trouble in infants with congenital atresia and there have been some interesting observations on this.

With regard to Dr. Crystal's comment about the prompt recognition and intervention in patients who do not do well, I would like to quote briefly from Tom Paine at the time of the American Revolution, when he said, "These are the times that try men's souls."

Carcinoma of the Lung

LAWRENCE B. KIRILUK, M.D., *Seattle, Washington*

From King County Hospital, Seattle, Washington.

THE great concern regarding carcinoma of the lung has centered about the increased incidence and the various agents which may be involved in the etiology of the disease. Our friends, the trial lawyers, are helping us to straighten out part of our confusion as to the exact nature of the role of certain agents in the etiology of the disease. The propaganda by both the medical and lay press to the public about early symptoms of cancer, has, at times, become a form of scaremongery and has encouraged the development of hypochondriac fears in a good many people. Yet, what better way is there to focus attention on a dreadful disease? From the surgical point of view this literature might be more justifiable if the early symptoms were not vague and liable to be produced by other diseases, or if we had good treatment to offer. As we all know, there has been very little change in the survival statistics or the rates of cure within recent years. However, regardless of whether or not the increased incidence is real or disproportionate to all other cancers, or whether it is still continuing, the present level is sufficiently high to make lung cancer a major problem for concern and investigation in the proper circles. Thus, the battle must go on. In prevention, if this were possible, surely lies the cure. At present, we must use the tools available to treat that which we, as yet, cannot prevent.

The over-all end results of the treated and untreated cases of bronchogenic carcinoma are poor. However, there are reports in the literature which are encouraging [*1–3*]. To get a firsthand look at the home front, a study was undertaken to review a series of consecutive cases observed at the King County Hospital during a twenty-year period, 1940 to 1959. It must be remembered that the cases being presented are selected under adverse circumstances, and the end results must be viewed as an outcome due to that selection and not to any serious deviation from the current methods of treatment. The County Hospital serves only indigents and, therefore, the patients are older, predominantly male and are in relatively poorer general physical condition than those presenting to private care. Also, there has been no elimination of terminal cases as may occur automatically at the prereferral level in private care.

SERIES PRESENTATION

During the twenty year period, there were many patients suspected of having carcinoma of the lung and in approximately 1,000 cases a clinical diagnosis of carcinoma of the lung was made. Of this group there were 443 proved cases of carcinoma. The diagnosis in these cases is supported by positive microscopy on tissue obtained by either bronchoscopy, surgery or postmortem examination. Six patients were lost to follow-up; none had undergone surgery. Complete follow-up studies are available on 437 patients. This includes 268 postmortem examinations. Statistics are often used to support theories, recommendations or conclusions. They can be arranged in such a fashion as to reflect the popularity or success of a clinic or specialist. They may at times reflect prejudice, a "human frailty," of an individual intensely interested in a certain method, procedure or disease. The figures to be presented here will be impartially factual since they do not represent a personal series. The greater portion of the care involved in this series was performed by the resident staff under the careful supervision of experienced staff personnel.

There were 395 men and forty-five women; fifteen patients were Negro and ten, Japanese. The serology was reactive in approximately 15 per cent of the cases. Approximately 6 per cent had or had had tuberculosis. Interestingly, twenty-seven patients, or about 6 per cent,

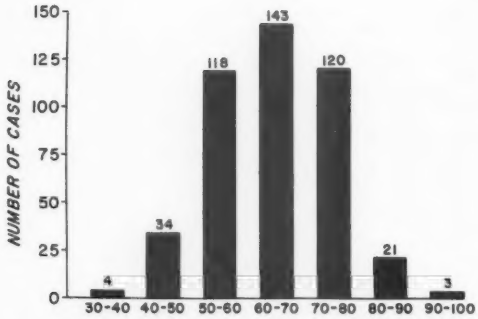

FIG. 1. Age distribution (range thirty-three to ninety-four years).

listed their occupation as cook. Might their disease possibly relate to their smoky, hot and greasy habitat during working hours? Approximately 95 per cent of the patients smoked and approximately 85 per cent used alcohol.

The average age was sixty-seven years. (Fig. 1.) The youngest patient was thirty-three years old and the oldest was ninety-four. The age was somewhat higher than the average age in reported series [3,4].

Eighty-two per cent of the patients presented with complaint of having a cough. (Fig. 2.) The average duration of symptoms prior to presentation was eight months. Seventy per cent claimed weight loss. Fifty-three per cent complained of chest pains not related to the myocardium. Forty-six per cent complained of a productive cough. Forty-three per cent complained of dyspnea. Thirty-eight per cent complained of hemoptysis. Thirty-three per cent complained of anorexia. The severity and duration of the signs and symptoms varied greatly. However, there was an average time lapse of eight months from the time of onset of symptoms to the time the patient first sought medical attention.

There occurred an average time lapse of thirty-eight days between the time that the patient was first seen and the time that a tentative clinical diagnosis of carcinoma was made. There were thirty-two cases in which the diagnosis was made at the time of postmortem examination and not suspected before that time. Two-hundred seventy-six patients were bronchoscoped. (Fig. 3.) The average delay between the time of clinical diagnosis of carcinoma and bronchoscopy was twelve days. Of the 276 patients examined by this method, the bronchoscopist made a diagnosis of carcinoma in 200; he thought infection was present in eight and believed that sixty-eight were negative. Biopsies were obtained in 198 cases; these proved positive for carcinoma in 153 (77.2 per cent); carcinoma was suspected in ten and thirty-five were negative. In the reported series the diagnosis by bronchoscopy and biopsy is approximately 50 per cent [5–7]. The high incidence of positive diagnosis in this series merely indicates that the majority of patients when first seen had well advanced carcinoma.

It was possible to localize the origin of the lesion with reasonable certainty in all but sixteen cases. (Fig. 4.) It is noted that 54 per cent of the lesions originated in the right lung and 45 per cent in the left lung. Excepting the lesions arising in the main stem bronchi, it was found that 61 per cent originated in the upper

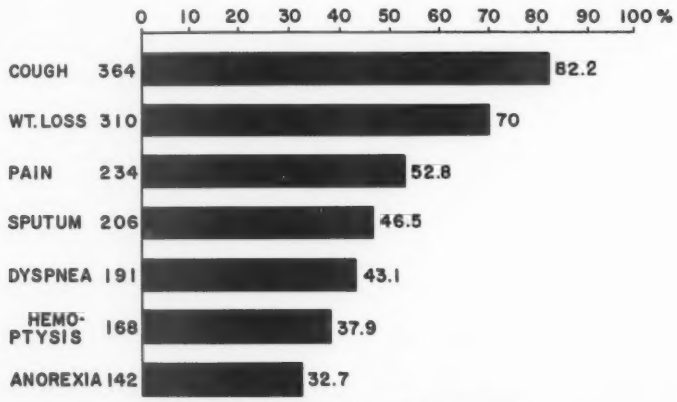

FIG. 2. Frequency of signs and symptoms.

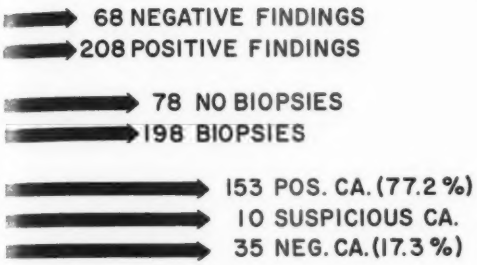

FIG. 3. Bronchoscopic results in 276 patients.

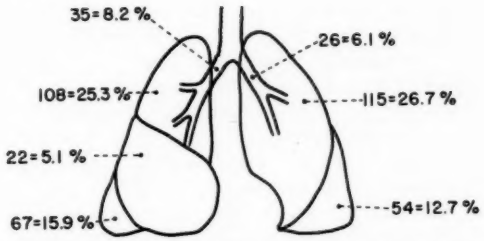

FIG. 4. Distribution of lesions within the lung in 427 cases.

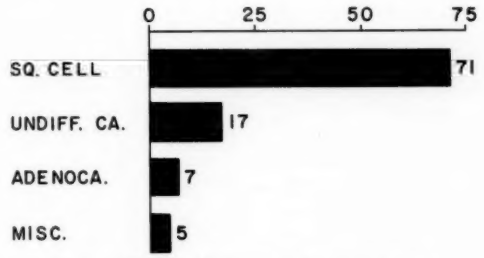

FIG. 5. Histiologic patterns, in percentages.

lobes and 39 per cent in the lower lobes. Histologic classification was not unusual [6,8]. (Fig. 5.) Seventy-one per cent of the lesions were squamous cell in nature; 17 per cent were undifferentiated in character; this included the anaplastic carcinomas. Seven per cent were well differentiated adenocarcinomas. Five per cent were in a miscellaneous group including oat cell, small cell and the alveolar cell carcinomas.

The vicious nature of this disease is realized when one considers the frequency of widespread metastases. It was found that metastases had occurred in 284 of 314 cases adequately examined. The hilar and mediastinal nodes, the liver, adrenals, bones, kidneys and brain were most often involved.

Two-hundred sixty-two patients received no treatment. (Table I.) They were seen on an average of 7.9 months after the onset of symptoms and lived an average of eleven months after the first sign or symptom. Thirty-eight patients received irradiation but fourteen were considered as inadequately treated or their treatment was discontinued for various reasons.

TABLE I
COMBINED RESULTS (437 CASES, SIX LOST TO FOLLOW-UP)

Treatment	No. of Cases*	Lived after Treatment (mo.)	Total Life after Onset (mo.)
None	262	...	11.2
X-ray	38	6.0	13.4
N_2 mustard	22	1.5	9.4
Surgery			
Thoracotomy	42	7.0	14.5
Resection	73	15	23

* Eleven still living.

Irradiation was used in four additional cases in which resection had been performed and was considered palliative, or in which recurrence had taken place.

Twenty-two of the patients had received nitrogen mustard as a palliative measure. They lived an average of 1.5 months after treatment.

One hundred fifteen patients (26 per cent of total) were subjected to surgery. (Table II.) Forty-two of these were subjected to explora-

TABLE II
FOLLOW-UP ON 115 SURGICAL CASES

42 Thoracotomies; all have died
  3 Postoperative deaths
  39 Died; average 7 months after surgery (1–22 mo.)
19 Lobectomies
  6 Postoperative deaths
  6 Positive nodules at surgery
  7 Negative nodules at surgery
    12 Died; average 14 mo. (2–26 mo.)
    1 Alive and well after 2 yr.
54 Pneumonectomies
  16 Postoperative deaths
  14 Positive nodes at surgery
    2 Alive and well after 11½ and 6½ yr.
    12 Died; average 7 mo. (2–14 mo.)
  24 Negative nodules at surgery
    16 Died; average 15.4 mo. (2–58 mo.)
    8 Alive and well (two—9½ yr.; one—5 yr.; two 4 yr.; one—3 yr.; two—2 yr.)

tory thoracotomy only. There were three postoperative deaths and the remainder all died at an average of seven months postoperatively.

The other seventy-three cases were operable but in thirty-one instances the procedure was considered palliative or positive lymphadenopathy was found at the time of surgery. There were nineteen lobectomies and fifty-four pneumonectomies performed. Of the nineteen patients having lobectomy, six died in the postoperative period. Seven of the remaining thirteen had negative nodes at the time of surgery. Twelve have died at an average of fourteen months postoperatively (range four to twenty-seven months). One is alive and well without recurrent disease at two years after surgery. Fifty-four pneumonectomies were performed with sixteen postoperative deaths resulting. At the time of surgery, fourteen had positive lymphadenopathy. Twelve of these have died at an average of seven months (two to fourteen months) postoperatively. Two remain alive and well at six and one-half and eleven and one-half years postoperatively. Twenty-four had negative nodes at the time of surgery and sixteen of these have died at an average of fifteen and four-tenths months (two to fifty-eight months) postoperatively. Eight remain alive and free of apparent disease. There are two cases living at nine and one-half years, one at five years, two at four years, one at three years, and two at two years postoperatively. Thus, there are five patients living over five years after pneumonectomy. No patient has lived five years and then died.

COMMENTS

The entire picture of carcinoma of the lung as presented here is not strange to us. In the series presented, only eleven patients of 443 remain alive; five of these are living over five years postoperatively. In the most recent years we have not seen a great revolution in the general end results of comparable determinate series. There will always be difficulties associated with this disease since the majority of patients fall into the age group of fifty years or older. The incidence of associated diseases is increased and, therefore, the application of therapy must of necessity be limited in many cases. Unfortunately, the most frequent first symptom is a cough. This symptom is so frequent in the general population that the true consequences can be overlooked in the patient with carcinoma. Also, despite education and ease or availability of medical attention, there is a certain percentage of the population which will procrastinate in the use of available facilities for an undetermined length of time. This is exemplified by the fact that in this series there were seventy-two patients of the 443 who died within eight days after admission to the hospital.

When one studies the large collected series or if one summarizes the literature in general, it is noted that about 50 per cent of the patients with carcinoma of the lung are operated upon [*5,7–9*]; that about 50 to 60 per cent [*5,8*] of these cases are resectable; that about 50 per cent of the resectable cases are considered curable; and that about 25 to 30 per cent of these survive five years [*9*]. Thus, the final percentage of five year survivals for the total group of patients with recognized carcinoma of the lung is less than 5 per cent [*4*].

In this series 26 per cent of the total were operated upon. Sixteen per cent were considered operable and 10 per cent were considered as having curative operations. The five year survival rate is about 1 per cent. This reflects, I think, what can be expected in a series collected in a county hospital for the reasons already stated.

An analysis of the surgical series reveals several facts. First, the percentage of surgical candidates is low and second the mortality rate is high (30 per cent of resectable cases). This reflects the generally poor condition of the surgical candidate. There was some improvement in the mortality rate during the second ten years, but the percentage of operable cases remained the same. A review of the cases subjected to lobectomy revealed that the majority of those were performed as a palliative procedure or because of necessity in patients with poor pulmonary function. Thus, lobectomy was not used in the "best candidates" in this series. The results verify this.

Of the patients subjected to pneumonectomy, two of fourteen with positive nodes survived five or more years and three of twenty-four with negative nodes have survived 5 or more years. This fact may bear out the importance of vascular invasion and blood stream metastases as has been recently reported [*9,10*].

It was of interest to attempt to determine why the five year survivors lived. It was found that the ten who survived longest all had peripheral lesions. One lesion measured 8 cm. in diameter and the remainder measured under

5 cm. in diameter. None of the lesions encroached upon their respective main stem bronchus. Seven of the lesions were well differentiated squamous cell carcinoma; two were adenocarcinomas; and one an undifferentiated carcinoma.

On considering the entire picture of carcinoma of the lung in a series such as presented here, it may be that more people would benefit and as many "cured" if lobectomy were used more often. Bronchoplastic procedures, such as reported by Paulson and Shaw [2], could be used as ancillary measures. Thus, many patients who were declared ineligible because of respiratory function studies could be given the opportunity of surgery. Also, if vascular invasion is as important as stated, than a more extensive operation such as a pneumonectomy is of no benefit in a large percentage of cases.

We would all certainly agree that there are possibilities for improvement in our management of this disease. Improvement must come from one of three avenues: (1) actual earlier diagnosis, (2) a more aggressive surgical approach, or (3) the development of some type of new therapy. The term, "earlier diagnosis," is used by everyone who discusses cancer. Some writers are trying to convince themselves and everyone else that earlier diagnosis would correct the entire situation as regards the low rate of surgical successes. There are two important facts to remember regarding the term, "earlier diagnosis." First, earlier diagnosis and cure are not synonymous and, second, there is a great difference between actual and theoretical early diagnosis. These facts are more easily appreciated if one remembers that a 1 cm. nodule of tissue contains about 60 million cells. It is also well to remember the statement, "there are no early specific symptoms for carcinoma of the lung." This means that the so-called earlier asymptomatic lesion can be diagnosed only by careful x-ray examination. About three years ago, Doctor Leo Rigler [11] presented a series of one hundred cases studied in retrospect and showed that over 50 per cent of the cases so studied showed x-ray evidence of disease more than two years prior to either the onset of symptoms or to the establishment of a definite diagnosis. He also showed that many of the lesions started peripherally and advanced medially. X-rays of the chest are readily available and, due to the contrast radiability of the lung fields, abnormalities are readily noted. The recent mass public chest x-ray program has opened up an avenue for the diagnosis of silent lesions. These lesions are extremely important in that if each such lesion were viewed with suspicion and if in the proper cases thoracotomy could be obtained, the cases of carcinoma subjected to extirpation would be increased. These are the cases most suitable for increasing the percentage of so-called cures.

In recent years therapy has not undergone any sensational revolution but it has improved. Our evaluation in each case is better. The availability of bronchoscopy and bronchoscopic biopsy has increased within recent years. The introduction of the scalene node biopsy has aided greatly in the selection of cases for surgery. Sputum smears and cellular studies are more frequently made and are undertaken by more experienced personnel.

In actual therapy the chemotherapist has made little gain. Many chemicals have been tried and are of questionable value. The most recent attempt has been progressing along the experimental use of drugs such as nitrogen mustard, before, during and after surgery. The results of this type of work shall have to be awaited. The radiotherapist has been able to alleviate some of the symptoms for variable periods of time but, in general, cure by x-ray therapy has not been successful. Surgeons have been reducing the operative mortality and are thereby increasing the only opportunity for durable treatment which, so far, has been made in this disease. They are aided by the internist and pulmonary physiologist in better cardiorespiratory evaluations, by the anesthesiologist in better and safer anesthesia. Thus, larger and safer operations can be devised. One can undertake extrapleural pneumonectomies or pneumonectomies with or without mediastinal node dissections or contralateral node dissection. Resection of the major bronchus or carina can be performed with reanastomosis of the remaining bronchial tree. It is to be remembered, however, that one's ability to perform an extensive radical extirpative procedure is not a criterion for the use of that procedure in all cases. It is believed, however, that the excision of suspicious peripheral pulmonary lesions which are undiagnosed, particularly in the patient who is asymptomatic, will be the most rewarding of all therapy for carcinoma of the lung. Apparently this is, as yet, a new idea and one unacceptable to many surgeons. However, these same surgeons will, without

question or undue delay, explore the breast, the abdomen or any other part of the body when there is a suspicion of malignancy. As an example, approximately 10 per cent of gastric ulcers are proved to be malignant; yet, after a short medical trial these are explored and resected. Possible malignancy is often the only basis for early resection. At the same time, approximately 25 per cent of the solitary nodules in the lungs, when other sites of malignancy are ruled out, prove to be malignant [12,13]. Although the condition of many of these patients is kept under surveillance, it is believed that there is a need to exercise the same precautions regarding the urgency of learning the exact nature of unexplained, but carefully considered, nodular shadows found in roentgenograms of the chest in persons who have reached the age in which the incidence of lung cancer is high.

There are many patients whose symptoms are not severe and who are best left untreated. There are a few for whom some form of treatment must be given for the sake of morale alone. In these circumstances, regardless of whether the physician is a surgeon, radiotherapist or a family doctor, it seems that his first duty to his patients with lung cancer is to bring them as much comfort of mind and body as he may and be quite certain that he does not add to their difficulties or distress. For this purpose he requires a clear idea of what he can achieve with treatment and a discerning eye for the person in whom the attempt should be made. If he decides to treat one symptom, he should do it with as little waste of time as possible because these patients have little time to waste. Most of his valuable work can be performed in consultation with the patient and relatives. The help resulting from kindness and patience and an appreciation of the value and the right moment for using heroin, morphine or cocaine may be more helpful to these people than the suggestion of a surgical extirpation or precise ideas about how many hundreds of roentgens they may require in how many days.

In conclusion, there are, I think, several things to remember: (1) that the over-all five year survival rate for carcinoma of the lung is poor and is less than 5 per cent of the total cases; (2) that the course and prognosis of an individual patient with bronchogenic carcinoma depends on the cell type, and its biologic activity, the host's resistance, the location in the lung and the time factor; (3) that the so-called terminal cases not be abandoned as they often are but that they be given supportive care; (4) that a more aggressive attitude should be taken by everyone toward the silent lesions of the chest, taking care not to make the mortality rate higher in the investigated cases than the increase in the five year survival rate of the patients with carcinoma of the lung found in this manner.

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DISCUSSION

Lyman A. Brewer, III (Los Angeles, Calif.): Dr. Kiriluk has presented a very searching analysis of the experience with carcinoma of the lung at the King County Hospital in Seattle. He has emphasized the low salvage rate with late diagnosis and the importance and meaning of early diagnosis. The findings in this report parallel our experience at the Los Angeles County General Hospital. However, in my series of private cases there has been an opportunity for earlier diagnosis. This afternoon I

will confine my remarks to a consideration of early diagnosis based on a study of these cases. In only 25 per cent of the cases in our series were the bronchoscopic findings positive while in Dr. Kiriluk's group 50 per cent were positive, indicating the much more advanced cases in his series. Furthermore, the symptomatology in his series was marked as compared with ours.

Since results of bronchoscopy are positive in only 25 per cent of cases treated at an earlier time, x-ray assumes a great importance. In a study of 570 cases, 352 of which were explored, we have arrived at a topical classification which is practical and helpful in understanding early diagnosis of carcinoma of the lung. This simple classification includes main bronchus, lobar bronchus, midlung and subpleural cancer. Examples of these four main types are as follows:

Main Bronchus Carcinoma. The bronchoscopic findings are always positive, onset of symptoms is early, and there may or may not be a mass present on early x-ray photograph at the hilum. The late findings are those of occlusion of the bronchus with atelectasis, pneumonitis and lung abscess. This group makes up 24 per cent of the explored cases.

Lobar Bronchus Carcinoma. The bronchoscopic findings may be positive. They are usually not positive early. However, most often there is a small parahilar mass revealed on taking of x-ray film. Obstruction of the lobar bronchus with pneumonitis, atelectasis and a lung abscess appear later. Fifty-four per cent of the cases operated on fell into this category.

Midlung Carcinoma. Midlung carcinoma was present in 11 per cent of the series. There are no early symptoms at all and the diagnosis is made entirely upon a shadow present in the x-ray film of the chest. Later on we have the symptoms of recurrent, persistent pneumonitis, localized atelectasis and localized emphysema. Bronchoscopic findings are never positive and are indicated only to determine bronchial or carinal extension.

Subpleural Carcinoma. Eleven per cent of the cases operated on were in this group. The results of bronchoscopy are always negative and have little value from the diagnostic standpoint. Early findings consist of a subpleural shadow and symptoms of pleurisy. Later on there is severe intercostal pain and massive secondary bloody pleural effusion at which time the lesion is usually inoperable.

This classification we found was important not only from the diagnostic standpoint, but also from the prognostic point of view as well. Resectibility in the midlung lesions was 95 per cent; in the main and lobar bronchus 50 per cent and in the subpleural only 42 per cent. There was an over-all 8 per cent mortality, 4 per cent for the lobectomies and 10 per cent for the pneumonectomies.

The follow-up according to this classification is of interest. Of the patients with midlung carcinoma, 16 per cent were dead at the end of the first year, 20 per cent of those with main bronchus and lobar carcinoma and 42 per cent of those with subpleural carcinoma. Other factors, including blood vessel invasion and cell type, although important, are outside the time limits of my discussion this afternoon.

We agree with the author in believing that the approach to improving the present results of treatment of lung cancer lies in earlier diagnosis. The ideal time to make the diagnosis is when the lesion is asymptomatic. The only way this can be done is with repeated x-rays in persons who are heavy smokers. The low yield of positive results in some mass x-ray surveys has shown that it is probably not economically feasible to survey the entire population. However, we believe that every male over the age of forty who is a heavy smoker should have a roentgenogram of the chest every six months. I am sure that will result in a higher yield than will general surveys, because 95 per cent of our cases and those in the authors' series were heavy smokers.

Two patients who had early asymptomatic carcinoma of the lung with four and ten year survivals following resection help to make our point. The preoperative shadows on their chest x-rays were 7 and 16 mm. in diameter respectively A study of these and similar cases makes it obvious that we must take these small lesions seriously. Active tuberculosis, coccidioides and the other granulomas should be excluded if possible. However, all doubtful cases must be treated by prompt resection. The resection of an early granuloma of the lung usually results in a cured patient if proper follow-up treatment is carried out. Furthermore, both the surgeon and the patient are relieved of the terrible worry of possible lung cancer. The resection of an early tiny cancer offers excellent chance of long time cure. Thus, resection of early asymptomatic lesions and those in which the symptoms are not severe must be our approach until that happy day arrives when we have an effective specific for cancer which will stop the growth of the malignant cells and destroy them wherever they are in the body.

LAWRENCE B. KIRILUK (closing): There is not much more to be said about carcinoma of the lung based on current knowledge. In conclusion I would like to summarize in this way: Surgery, of course, offers no answer to the problem of cancer; however, at the present time it is the best form of treatment for the patient suffering from carcinoma of the lung, and until a better way is found, there is every justification for extending our recommendation for surgery to include such extensions of disease that are within the competence of removal, for none can judge at the time of operation which patient will or will not have a long survival apparently free of disease.

Regional Blood Flow in Hemorrhagic Shock

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THIS STUDY represents an attempt to help clarify the relationships between various degrees of acute hemorrhage and regional blood flow. The real measure of the degree of shock in a given situation is the quantitative regional flow of oxygenated blood in relation to tissue metabolic needs. It follows that the relationship between regional blood flow and clinical manifestations of shock such as hypotension should be of practical interest.

The circulation of blood to the vital organs during hemorrhagic shock has been extensively studied, but much of the data obtained are based on experiments utilizing profound degrees of hypovolemia. Also, until recently, determinations of blood flow have been made by indirect methods which require division or cannulation of vessels. Some of these methods depend upon the functional integrity of the organs being studied which makes the results subject to errors related to disturbed cellular function from the ischemia induced by the experimental shock itself. This group of experiments was designed to study the changes in regional blood flow, blood pressure and cardiac output incident to mild and moderate degrees of hypovolemia.

Blood flow measurements were made with a square-wave electromagnetic flowmeter designed by Denison and Spencer [5]. The use of instruments of this type permits the direct measurement of flow without division or cannulation of the blood vessels concerned. Among the basic principles involved in flow measurements with the electromagnetic flowmeter is that a stream of blood moving through a vessel acts as a conductor of electricity. An external magnet device known as a "probe" is placed snugly around the vessel creating a constant magnetic field. When the blood stream travels through this magnetic field, a detectable voltage is induced which is registered in terms of flow per unit of time on a suitable recording device such as a Sanborn polyviso recorder. The flowmeter is previously calibrated by passing blood at carefully measured rates through blood vessel segments. Besides certain advantages of the electromagnetic flowmeter in animal experiments, it is applicable to human beings in that no disruption of blood vessels is required for its use. (Fig. 1.)

METHODS

Fasting adult mongrel dogs, varying from 15 to 20 kg. in weight, were lightly anesthetized with intravenous pentobarbital sodium. The femoral vessels were exposed and cannulated on one side for the measurement of arterial blood pressure and for the withdrawal of blood to produce experimental hemorrhage. The femoral vessels were exposed on each side when both cardiac outputs and femoral blood flows were to be determined. The various other arteries to be used for blood flow measurement were likewise carefully exposed and isolated to facilitate proper placement of the electromagnetic flowmeter probe. Arterial blood pressures were obtained with a Statham strain gauge and the blood flows with the square-wave electromagnetic flowmeter. The arterial blood pressure and the blood flows were monitered continuously during the experiments. Cardiac outputs were determined by a dilutional technic using Renografin® as described by Crane, Adams and Woodward [3]. A multichannel Sanborn polyviso recorder was used to record these various determinations.

In each experiment after physiologic stability was reached and suitable control values obtained, the animals were subjected to successive

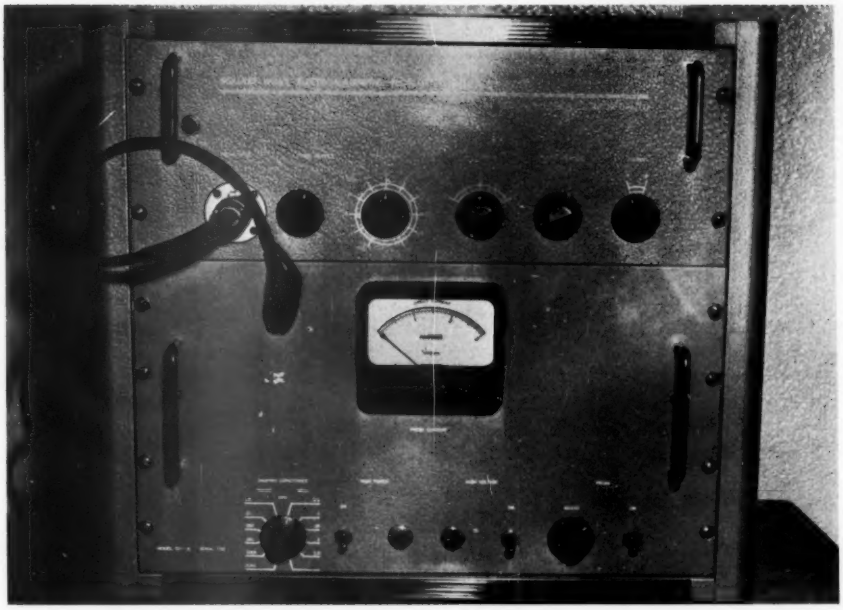

FIG. 1. Illustrated above is the square-wave electromagnetic flowmeter unit used in these experiments. The "probe" is displayed on the left side of the instrument.

degrees of brisk hemorrhage; 10 per cent of the calculated original blood volume being withdrawn each time. In all animals the depth of hemorrhage was carried to at least 20 per cent and in some instances to 40 and 50 per cent. After each episode of hemorrhage the animal was allowed to stabilize while determinations were made before the induction of further bleeding. Wherever percentage decreases in blood pressure, cardiac output or blood flow are expressed, they represent change from the original control values. In each animal at the conclusion of the hemorrhage experiment, the withdrawn blood was replaced or the blood pressure was restored with some vasopressor (such as Aramine®) and further observations made.

RESULTS

The effects of hemorrhage on the cardiac output in eleven dogs are summarized as follows: a 10 per cent hemorrhage produced a 21 per cent decrease in cardiac output, and a 20 per cent hemorrhage produced a fall of 45 per cent. The percentage fall in blood pressure was only one third of the percentage decrease in cardiac output or 7 and 15 per cent, respectively. The mean control blood pressure was 125 mm. Hg.

The effect of acute hemorrhage on carotid artery flow in ten dogs is summarized as follows: the 10 per cent hemorrhage resulted in a 28 per cent decrease in flow while the blood pressure fell only 7 per cent from the control value. The 20 per cent blood volume reduction produced a 51 per cent decrease in carotid flow, while the blood pressure fell only 15 per cent. In several animals the blood pressure was returned to the control level (125 mm. Hg) by an intravenous vasopressor drip. It was possible to raise and maintain the blood pressure with small amounts of the vasopressor, but the carotid blood flow consistently remained severely reduced. However, when the blood pressure was brought to control levels by blood volume replacement, the blood flow promptly returned to the control value. The average unilateral control flow was 10 ml./kg./minute (the range was 5 to 18 ml.).

Following are the results of acute blood loss on femoral artery flow in five dogs. A sharp decrease of 38 per cent in femoral flow occurred with the 10 per cent hemorrhage (the blood pressure fell 9 per cent); with a 20 per cent blood

TABLE I
THE EFFECTS OF ACUTE HEMORRHAGE ON UNILATERAL RENAL ARTERY FLOW IN EIGHT DOGS

Hemorrhage (%)	Decrease in Blood Pressure* (%)	Decrease in Blood Flow† (%)
10	7	6
20	15	17
30	27	28
40	36	47

* Mean control blood pressure was 130 mm. Hg.
† Average control flow was 10 ml./kg./minute (range was 7 to 14 ml.).

TABLE II
THE RESULTS OF ACUTE HEMORRHAGE ON HEPATIC ARTERY FLOW IN SEVEN DOGS

Hemorrhage (%)	Decrease in Blood Pressure* (%)	Decrease in Blood Flow† (%)
10	6	6
20	11	17
30	24	34
40	38	49
50	59	66

* Mean control blood pressure was 127 mm. Hg.
† Average control flow was 13 ml./kg./minute (range was 10 to 21 ml.).

loss there was a 60 per cent reduction in flow (blood pressure dropped 17 per cent). When the blood pressure was restored with vasopressors, the femoral artery flow remained at 50 per cent of normal. The average control flow was 5 ml./kg./minute (the range was 4 to 8 ml.). The mean control blood pressure was 130 mm. Hg.

The response of the mesenteric artery flow to acute blood loss in ten dogs is outlined as follows: There was a reduction of 27 per cent in flow following a 10 per cent hemorrhage, and a sharp decrease to 50 per cent artery flow occurred when the blood loss was increased to 20 per cent; the accompanying blood pressure reduction was 4 per cent and 12 per cent, respectively. Again a definite contrast between the fall in blood pressure and a more profound drop in blood flow was observed. When the blood pressure was restored with vasopressors, the mesenteric blood flow usually remained sharply reduced. The average control flow was 19 ml./kg./minute (the range was 14 to 29 ml.) and the mean control blood pressure was 128 mm. Hg.

Table 1 shows the renal blood flow response to hemorrhage varying in degree from 10 to 40 per cent of the blood volume in eight dogs. The reduction in blood flow closely parallels the reduction in blood volume and blood pressure in contrast to the situation in the carotid, femoral and mesenteric vessels in which the flow reduction was proportionately much greater. With a 40 per cent hemorrhage, the blood pressure fell 36 per cent and the renal blood flow dropped to 47 per cent of the control level. With restoration of blood pressure by vasopressors in certain animals the renal blood flow remained depressed at 45 per cent below normal, in contrast to prompt restoration of renal flow when blood replacement was used instead of vasopressor agents.

Table II outlines the effects of hemorrhage varying in degree from 10 to 50 per cent on the hepatic artery flow in seven dogs. As in the case of the renal artery, the percentage decrease in hepatic flow approximated the percentage drop in blood pressure. When the control level blood pressure was restored with a vasopressor, the hepatic artery flow frequently remained profoundly reduced.

Whenever the reduced blood pressure in these animals was brought to normal levels by replacing the lost blood volume, the regional blood flows promptly returned to or near control values. This was in sharp contrast to blood pressure restoration with vasopressors in which regional blood flow frequently remained persistently reduced, often to profoundly low levels. In certain animals the blood pressure was brought to normal with vasopressors and then the previously withdrawn blood was transfused back restoring the calculated blood volume. When this was executed acute pulmonary edema and death frequently resulted.

COMMENTS

Cannon and his associates [2], using a sine-wave electromagnetic flowmeter, recently emphasized the measurement of blood flow as an important key in the understanding of circulatory physiology and problems of circulation. They pointed out that blood flow cannot necessarily be inferred from pulse rate and blood pressure. Schenk and others [6] have

used the electromagnetic flowmeter to determine blood flow in various vessels at the time of peripheral arterial surgery in human beings, and their preliminary observations suggest that much may be learned by this approach. It appears that the use of such noncannulating electronic measuring devices may result in the modification of many current concepts regarding the relationship of blood pressure, vessel lumen size, blood volume, peripheral resistance and actual blood flow.

There is a minimum of data currently available on normal blood flows in the dog as determined by the electromagnetic flowmeter method. According to Drapanas, Kluge and Schenk [*4*], the average hepatic artery flow in dogs under control circumstances with the electromagnetic flowmeter is 14 ml/kg./minute. This figure compares closely with our average control hepatic artery flow of 13 ml./kg./minute. Our unilateral renal flow was 10 ml./kg./minute which corresponds closely to the 9.2 ml./kg./minute unilateral flow reported by Stone and associates [*8*] using a different method. Bounous, Shumacker and King [*1*], with a still different method, found the total or bilateral renal flow to average 28 ml./kg./minute.

The data obtained from this group of experiments demonstrate that a significant reduction in regional blood flow may occur in response to relatively small amounts of acute blood loss. The blood flow reduction is especially pronounced in the carotid, mesenteric and femoral areas, whereas the renal and hepatic circulations retain a more substantial share of the cardiac output. The percentage reduction of the blood volume and the blood pressure in response to acute hemorrhage closely paralleled the percentage fall in blood flow in the renal and hepatic arteries. On the other hand, the percentage drop in blood flow in the carotid, mesenteric and femoral arteries is considerably greater than would be expected from the fall in blood pressure or reduction in blood volume.

This redistribution of the depressed cardiac output during hemorrhage is presumably accomplished by increased peripheral vascular resistance in certain areas such as the femoral, mesenteric and carotid, and by decreased vascular resistance in others such as in the renal circulation [*7*]. It is interesting to observe that the carotid artery which carries the chief blood supply to the brain acts like the femoral and mesenteric arteries in the presence of acute blood loss. These data suggest that the blood flow to the brain is not as well protected as, for example, the blood flow to the kidney. Blood flow to the liver in the presence of acute hemorrhage is still further decreased by the severely reduced mesenteric flow which presumably results in a sharp reduction in portal vein flow.

Preliminary observations on the effects of vasopressors (Aramine) on blood pressure and regional blood flow in acute hemorrhage emphasize that blood flow to vital organs is frequently not restored when the blood pressure is supported by vasopressors rather than by blood volume replacement. These observations seem to apply to all regional areas studied including the renal and hepatic circulations. It is interesting to observe the catastrophic situation which may result when vasopressors and volume replacement are injudiciously combined in the treatment of acute blood loss. These observations of the effects of vasopressors complement both clinical impressions regarding their use and experimental data obtained by others. Further studies are in progress with regard to vasopressor and vasodilator drugs in relation to regional blood flow in a variety of circumstances.

It is hoped that these observations will help focus clinical attention on regional blood flow to the vital organs as the most critical disturbance in hemorrhagic or hypovolemic shock.

SUMMARY AND CONCLUSIONS

1. Further experience is presented with the use of the electromagnetic flowmeter for the determination of regional blood flow.

2. Data are presented to show the effects of acute blood loss on regional blood flow in dogs. The percentage reduction in blood flow from control values is compared to the percentage fall in blood pressure and blood volume in animals having acute hemorrhage. The reduction in blood flow was especially severe in the carotid, mesenteric and femoral areas when compared to the fall in blood pressure, whereas the flow reduction was more proportional to the blood pressure in the renal and hepatic circulations.

3. The effects of acute hemorrhage on cardiac output were noted. The cardiac output fell more in proportion than did the blood pressure or blood volume.

4. Preliminary observations indicate that when the blood pressure is returned to control levels with vasopressors, the regional blood flow frequently remains severely reduced in all areas of the body studied.

5. Attention is focused upon regional blood flow to vital organs as the most critical disturbance in hemorrhagic or hypovolemic shock.

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DISCUSSION

William P. Longmire, Jr. (Los Angeles, Calif.): The introduction of the electromagnetic flowmeter by A. Kolin, W. G. Schenk, Jr. and others, as a device for measuring blood flow, has provided a most useful tool to be utilized in studying a variety of physiologic and pathologic conditions. This technic probably represents the most accurate method available today for the measurement of blood flow in a specific vessel. However, the vessel in which the flow is to be measured must be isolated and the probe securely applied to the vessel wall; it might be anticipated that such maneuvers would only slightly alter the basal conditions of flow in these vessels. Changes recorded in blood flow, once the vessel has been isolated and a probe securely applied, however, are probably of greater significance than is the attempted determination of a normal blood flow in these vessels.

The authors' finding of a smaller decrease in blood flow in the hepatic and renal arteries than that which occurs in the femoral vessel substantiates the view previously based on indirect evidence that, in conditions of shock, vasoconstriction is greatest in the peripheral vascular bed. This is an apparent effort on the part of the body to conserve blood flow to the important visceral structures.

In these studies it is most interesting that the flow in the mesenteric artery did not share in this so-called protective reaction, inasmuch as the studies of J. Fine and of R. Lillehei both indicate that in the dog the mucosa of the small intestine is more sensitive to hypoxia than is the liver or the kidney. Dogs in which the ascending aorta has been cross-clamped for certain periods of time will die, after release of the clamp, from loss of blood and fluid into and through the intestinal mucosa. On the other hand, when Lillehei perfused the superior mesenteric artery with oxygenated blood during the time the descending aorta was cross-clamped, the animals survived these periods of aortic cross-clamping without difficulty.

In Fine's experiments on so-called irreversible shock, the dogs also died with an edematous hemorrhagic enteritis and a bloody diarrhea. This type of intestinal mucosal sensitivity apparently is characteristic of the dog, and is probably, as some people have described, related to the bacterial flora of the dog's intestines. Apparently this condition is not observed in man. For instance, hemorrhage and edema of the intestinal mucosa and bloody diarrhea were not encountered in a single patient dying of traumatic shock during the Korean War.

As the authors have commented, it is also unusual that the blood flow in the carotid artery did not participate in this protective distribution of the cardiac output. I think that these findings might call into question the entire effectiveness of this so-called protective vasoconstrictive reaction.

Vasopressor substances increased the blood pressure but did not result in the restoration of blood flow to the various regions studied in these experiments. R. M. Nelson and J. W. Henry have recently reported similar results on the renal circulation following the injection of norepinephrine. On the other hand, the recent studies of A. D. Menno and Schenk are quite important in this regard because these investigators, using the electromagnetic flowmeter, noted that both epinephrine and norepinephrine produced a striking increase in the coronary blood flow.

One method of producing shock and death twenty years ago was used by P. B. Price, R. C. Hanlon and me on normal volemic dogs. This was the slow continuous intravenous infusion of epinephrine. J. V. Maloney, Jr. and K. Schmutzer have recently

demonstrated a marked loss of intervascular fluid and a reduction of blood volume produced by the prolonged administration of norepinephrine. These observations would all support the general clinical impression that in instances of hypovolemic shock, vasoconstrictor drugs are of temporary value for increasing coronary blood flow and improving cardiac action. Restoration of blood volume, however, is still the *sine qua non* for recovery in this type of shock.

In closing, may I comment on one further avenue that might be of interest and could be studied readily by this technic. Buried within the glamorous "lytic cocktail" and artificial hibernation induced by Laborite some years ago was a notion of abolishing the normal protective vasoconstrictive reaction to shock and supplanting this with vasodilatation. It was R. Laborite's idea that at times the protective action of vasoconstriction in the face of severe hypovolemia and hypotension actually became destructive rather than protective, and that vasodilatation which would permit a widespread capillary circulation to continue, even though at a markedly reduced flow, would increase the chances of survival in cases of severe shock.

After a brief wave of enthusiasm, particularly in Europe, this concept has been largely abandoned. However, a year ago in this country A. Boba published an article in which a series of cases was reported which support the view that in severe shock when all of the usual methods of treatment seem destined to failure systemic vasodilatation, produced by an injection of Arfonad,® was of value.

In animals in a state of shock, changes in blood flow produced by the injection of vasodilator drugs would be of interest and could be readily studied by technics just reported.

DAVID METHENY (Seattle, Wash.): There is one practical point which I saw demonstrated about fifteen years ago; I think that sometimes the distribution of vasoconstriction is also disturbed, not only regionally but between the arteries and veins. I was called to see a man in the county hospital who was hemorrhaging from a ruptured aneurysm in the iliac artery. We did not know what he had at first, and as I arrived members of the staff were attempting to give him blood intravenously. The bottle was 5 feet above the level of the patient, and the vasoconstriction of the veins was such that the blood would not run in gravitationally at this height. This was about 120 mm. of pressure that they were trying to get into the veins.

As we were watching this procedure the patient gave a gasp, his capillaries failed and he looked like he was dying; his skin became blotchy and blue and he became unconscious.

There was another unit of blood handy. A needle was inserted into the femoral artery and this container of blood was also put up about 5 feet above the level of the patient. The blood flowed into the femoral artery as though it were running onto the floor. As one would expect there was just no resistance at all. After about 250 to 300 cc. blood flowed into the femoral artery, the patient's blood pressure and color returned to normal, and he became conscious.

Then a curious thing happened: blood stopped running into the femoral artery because his systolic blood pressure was now over 120 mm. of Hg, and at which time the blood started running into the vein again.

It is one of the things I have remembered for a long time. The Russians did a lot of work with arterial transfusion in cases of severe shock during World War II. They revived people who they thought otherwise would not survive. I recommend this method to you.

ROSS ROBERTSON (Vancouver, B. C.): For many years I have been greatly interested in this subject. This report has brought out profoundly the fact that blood pressure is not a good guide for the anaesthetist in deciding whether or not the patient is going into shock. Blood loss must be replaced without waiting for a fall in blood pressure.

In the postoperative period we have found that the estimation of venous pressure is of tremendous assistance in the treatment of shock. If the venous pressure is low, blood can safely be added and the heart will handle the increased volume until the venous pressure comes up to at least 10 cm. water.

Citrated blood given rapidly in large quantities will often cause poor cardiac action from citrate poisoning. In this situation the response of the heart to the administration of calcium is dramatic.

Regarding the intestinal necrosis in dogs which has just been commented on by Dr. Longmire, we have also seen this occur in patients with aortic regurgitation who have had a temporary fall in blood pressure. There is massive intestinal necrosis without any evidence of thrombosis or embolism.

CLARENCE E. STAFFORD (Los Angeles, Calif.): The clinical implications from these facts that have been presented are most interesting. There is a question, of course, whether or not we can find an exact parallel situation in man as we have found in the dog, but, assuming that there would be some comparison, it is interesting to use as an illustration the case of a patient with gastrointestinal hemorrhage; for example, an elderly patient (seventy years of age) with a blood pressure of 150/90 mm. Hg who loses 2 to 3 pints of blood. This is roughly around 20 per cent hemorrhage or the same percentage given in our report.

This, then, would result in a 60 per cent decrease in blood flow through the peripheral vessels such as the femoral, and contribute to the high incidence of postoperative vascular problems in these

patients. We have found among this group an extremely high incidence of fatal pulmonary embolism, and the setting here certainly would provide for such a complication.

Then if this patient continues to lose a further 2 or 3 pints of blood, bringing him down to about a 40 per cent hemorrhage, renal and liver damage can take place because of the 50 per cent decrease in blood flow to these organs. Thus, it is easy to see how this patient, who perhaps already has some renal disease, may have further irreparable damage.

It is interesting to go into the realm of speculation but so far as the decrease in the cerebral blood flow is concerned, it can be hoped that man, being a higher order of animal life than the dog, is provided with some mechanism that may allow for better control of cerebral blood flow. From our clinical observations, we do see the patient with severe hemorrhage of the periphery or gastrointestinal tract which apparently contributes to cerebral vascular accident.

While the patient is suffering a degree of damage to the vital organs the blood pressure may have decreased only slightly. With a 60 per cent decrease in femoral flow the blood pressure may have only dropped from 150 to 125 mm. Hg systolic pressure, and with a 50 per cent decrease in flow to the kidneys, the blood pressure may have dropped to only 100 mm. Hg. We are hopeful that these observations can lead us to further information that will be helpful in dealing with these critically ill patients with hemorrhagic shock.

DAVID B. HINSHAW (closing): With regard to Dr. Robertson's question, the venous pressure was monitored throughout these experiments. The only significant venous pressure changes occurred when overtransfusion was in evidence or when certain animals had blood volume replacement after the use of vasopressors. High venous pressure readings generally were significant, but low or normal readings, in so far as the depth of shock was concerned, did not seem significant.

A Comparison of Methods of Treatment of Extensive Burns at the San Francisco General Hospital

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SEVERAL years ago I reported [2] on the treatment of burned patients admitted to the University of California Surgical Service from 1943 to 1956. In this series, ninety-three of 448 patients had more than 20 per cent of the body surface burned. (Fig. 1.) Only one patient in this fourteen year period survived with a surface burn greater than 45 per cent. This patient was a four year old child who was admitted in 1948 with a 65 per cent total burn and a 20 per cent third degree burn. Of patients 50 years of age or older, not one survived with a burn greater than 25 per cent.

It appeared that chances for survival were greatest in the cases which lie within the dotted line (Fig. 1), that is, patients who were less than 50 years old and who had burns of less than 45 per cent of the total surface. In this group the children who died succumbed from septicemia and the alcoholics who died succumbed from infection.

This study (Fig. 2) showed that the mortal-

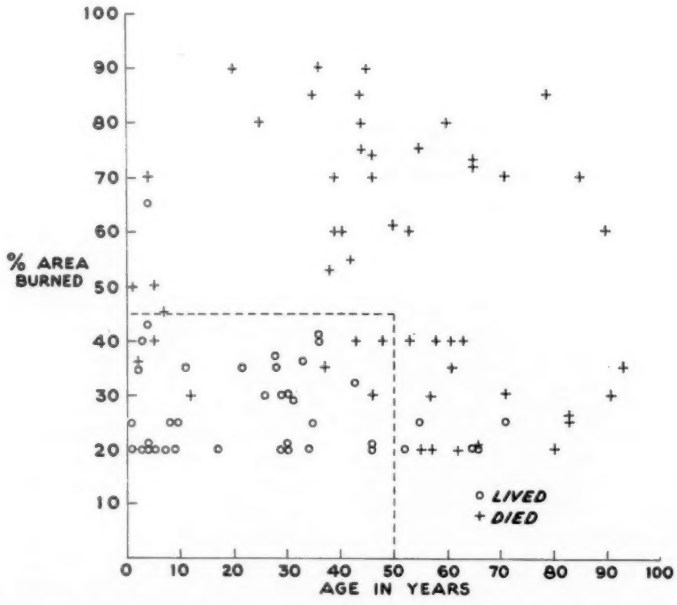


FIG. 1. Age as related to severity in burns of more than 20 per cent. San Francisco General Hospital 1943 to 1956.

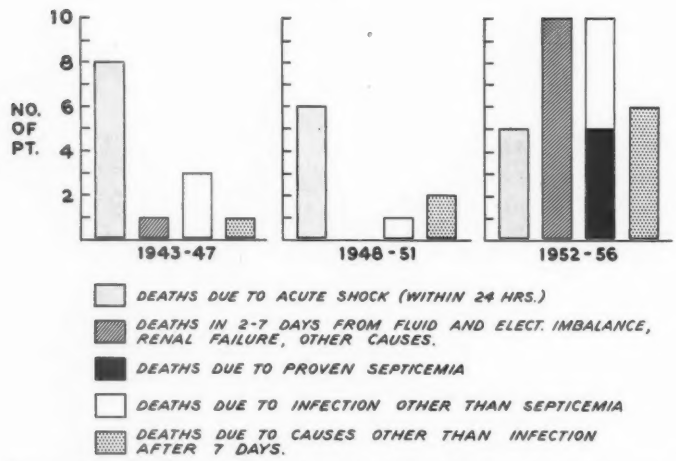


FIG. 2. Comparison by time periods of the causes of death in cases of burns of more than 20 per cent. San Francisco General Hospital 1943 to 1956.

ity was greater in the later years of the study. Deaths from burn shock markedly decreased, but the number of deaths occurring two to seven days after the burn sharply increased. These patients died from cardiac complications, acute renal insufficiency, or hepatic and renal changes. Although infection was of minor importance as a cause of death in the earlier group (1943 to 1947), 33 per cent of the patients in the later group (1952 to 1956) died from infection.

From 1943 to 1951 the wounds of burned patients were almost invariably treated with compression bandages applied over xeroform or vaseline gauze. From 1952 to 1956 the wounds were nearly always treated open. However, the difference in local treatment had little effect on mortality.

Patients admitted from 1943 through 1951 received variable amounts of plasma and little or no whole blood or electrolytes during the shock phase. From 1952 through 1956 the Evan's formula was followed fairly closely.

The general measures for combating sepsis were essentially the same throughout the period under study. Burns were treated on the open surgical ward or in side rooms in which some isolation measures were followed. Antibiotics were used both prophylactically and therapeutically in increasing amounts in the latter part of the study, but the number of deaths from infection steadily mounted. Most of the increased mortality was secondary to infection. Although we could partially justify the increased mortality by the fact that the average age of the patient had increased from forty-five to fifty-four, some drastic changes in treatment seemed necessary. The present report describes new types of treatment now being used on our two surgical services.

Folgelman and Wilson [3] have recently reported on the treatment with Ringer's lactate solution of experimentally produced burns in dogs as compared to treatment with colloids. They were able to show that measurable amounts of salt water may be lost into body tissues secondary to extensive burns, and that there is a critical need for salt water replacement. On the other hand, when blood transfusions are given as volume replacement during depletion of extracellular fluid volume, as in burns, irreversible pulmonary congestion and impaired renal function may result. Ringer's lactate solution was substituted in order to avoid the dilutional acidosis that would result from a large amount of sodium chloride. They were able to show that when a colloid is put into a water vehicle without salt no therapeutic effect could be shown. In fact the survival rate was less than with no treatment at all.

Wilson and Stirman [10] in a controlled series in which burned patients treated with blood and saline were compared to a series treated with Ringer's lactate solution and oral fluids found a statistically significant difference

in the mortality rates in the first ten days after the burn was sustained. In the group of patients with burns of 30 to 44 per cent of the body surface, there was a 27 per cent mortality in the first ten days in patients receiving blood as a part of the therapy for shock, as compared to a 4 per cent mortality for those receiving only a balanced salt solution. Markley et al. [4] in comparing two large groups of severely burned patients found a mortality of 12 per cent within the first two days in patients treated with blood, plasma or dextran, and no mortality in the first two days in patients treated with saline only. What explanations are given for this improvement in early mortality? Fogelman and Wilson in experiments on dogs found that respiratory insufficiency began shortly after burning, but when electrolyte solutions were given, respiratory function improved by the end of five hours. However, 70 per cent of dogs treated with colloids had a more marked respiratory insufficiency at the end of five hours. Vogel and Tumbusch [9] of the Brooke Army Burn Center suggested that blood may also play a part in the high incidence of infection. They stated that blood (in reality a large foreign body molecule) may set up a Shwartzman reaction, blocking the reticuloendothelial system and thereby obviate the body's defenses against infection. This theory would only apply to the deaths from infection, which occur usually after the first ten days. Vogel and Tumbusch state that they are still using colloids, that is, the Brooke formula.

As mentioned earlier, an increasing problem in our hospital is that of infection and of deaths from infection. The very young patient, the older patient (more than fifty years old) and the alcoholic have been particularly susceptible. As others have observed, a marked increase has occurred in the incidence of infections caused by gram-negative organisms, particularly Pseudomonas. Prophylactic antibiotics seemed to have little or no effect upon preventing infection or death from septicemia. In fact, none of the patients in whom septicemia developed survived in the group studied from 1943 to 1956.

What weapons do we have at hand to attack this problem of infection? Available therapy includes: (1) strict isolation of the burn patient; (2) antibiotics; (3) early grafting; (4) homografting.

Without question, strict isolation of the burned patient is necessary and advisable. However, despite the strictest kind of isolation Moncrief [7] reports a high incidence of infection at the Brooke Army Burn Center. Although we do not have a separate burn unit and our isolation is incomplete, it has been our belief that further isolation of patients would only lead to a very small improvement in our results. The organisms found in burn infections, primarily gram-negative, are not the organisms that are common on the open surgical wards.

The value of antibiotics in these burn infections is difficult to evaluate. As mentioned, they had no value when used prophylactically, and even when used therapeutically against infections of the blood stream, they seemed ineffective. In fact, in our early study no patient survived who had developed septicemia. Nevertheless, we are certainly still using antibiotics as will be discussed under treatment.

Many articles have been published which recommend early grafting. Meeker and Snyder [6] reported on a group of children in whom the burns were debrided early with an electric dermatome and who were then autografted several days later. It has been our impression that patients with massive burns do not tolerate the taking of extensive autografts. We have reserved the early excision of third degreee burns and subsequent autografting procedures to third degree burns of the hand and to relatively small burns (under 20 per cent).

On the other hand, the best dressing for a burn is skin, even someone else's skin. Homografting in our experience has been of real value.

PRESENT METHOD OF TREATMENT

Burn patients at the newly reorganized San Francisco General Hospital were divided into two groups, Group A and Group B. Patients are admitted into each group in an alternate manner so that the groups each have approximately the same number of patients in each age category, the same number of alcoholics, and so forth. The patients in Group A are treated in the same manner as described in the earlier report [2]; they were given the Brooke formula (colloids and electrolytes) during the shock phase and were autografted when the burn eschar separated (twenty-two to twenty-six days); antibiotics were used prophylactically.

FIG. 3. A, six year old girl on twelfth postburn day, 55 per cent, third degree burn. Treated with electrolytes only. B, one day after homografting, twentieth postburn day.

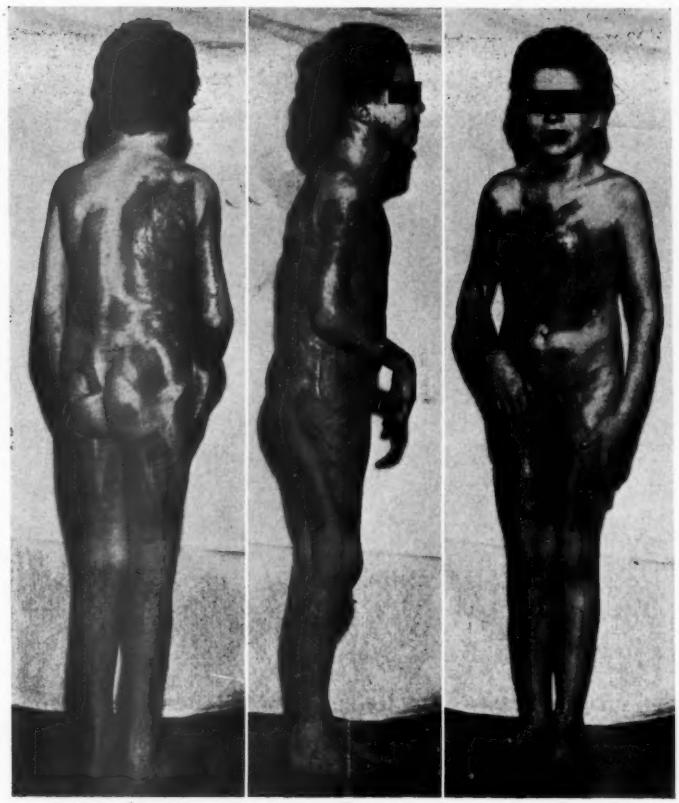
Certain specific differences are made in the treatment of patients in Group B. Instead of being given colloids and electrolytes during the shock phase, these patients were given only intravenous electrolytes, and oral electrolytes if they could be tolerated. Second, in extensive burns homografting was performed at a relatively early date. Third, the administration of antibiotics was carefully controlled.

Fluids are given in the following amounts, but may be adjusted depending on the patient's age, cardiac status and urinary output. Formula = per cent burn × kg. × 2 = amount of Ringer's lactate; plus 2,000 cc. 5 per cent dextrose in water. No burn is estimated to be over 50 per cent. As mentioned, patients are given oral fluids as soon as possible and "Moyer's solution" (3 gm. sodium chloride and 1.5 gm. sodium bicarbonate per L. of water) is used. No other fluids are given. Any fluids taken orally are subtracted from the electrolytes given intravenously. The above amount of fluid represents the total amount given in the first twenty-four hours. One-half the total amount is given in the first eight hours. During the second twenty-four hour period, the amount of electrolytes is decreased by half. Some patients will not tolerate oral fluids and may even become nauseated and vomit. A nasogastric tube is inserted until the nausea or ileus has been relieved. By the end of the second day most patients will tolerate surgical liquids. Because of one recent fatality due to hemorrhage from a Curling's ulcer, all burned patients are given antacids as soon as they begin taking fluid orally.

Patients with 60 and 70 per cent burns tolerate oral fluids quite early in the postburn period. Despite such early encouragement patients with such extensive burns usually died by the end of the first week; death was due to terminal pulmonary edema or kidney failure.

ANTIBIOTICS

Rather than become therapeutic nihilists the following method of administration of antibiotics has been developed in Group B. Penicillin and streptomycin are given in large amounts during the first forty-eight to seventy-two hours and are then discontinued. The *appropriate* antibiotic is then given: (1) if the patient develops a high fever with evidence of



A B C

FIG. 4. A, B and C, six year old girl with 55 per cent third degree burn on 147th postburn day. Contractures present in right axilla and right groin.

gross infection about the burn sites; (2) if a positive blood culture is obtained; (3) just prior to and following each grafting procedure. Sensitivity studies are most important in determining the *appropriate* antibiotic to use.

GRAFTING

Patients with extensive burns in any age group tolerate autografting procedures poorly and this is even more marked in the old, the very young and in alcoholics. The use of homografts should always be considered in these critically injured patients. In the past it has been customary to either debride the wound relatively early [6] and then wait a few days before applying homografts or to wait until all the burn eschar has separated, usually by the 25th day after the burn, and then apply homografts.

As the following case report will show, this patient was surgically debrided on the nineteenth day after burn and *immediately homografted.* Her general improvement was sensational and to our amazement most of the homografts took.

CASE REPORT

A six year old white girl was admitted to the University of California Service (Group B) on June 29, 1960. A few minutes previously approximately half of her body had been burned when her pajamas were accidently set on fire by her younger brother who was playing with matches. Examination showed that the burn covered approximately 55 per cent of the body surface, and was almost entirely third degree. (Figs. 3A and B.)

She was treated by the open technic. No prophylactic antibiotics were given on admission. Crystalloids were administered intravenously for the first

FIG. 5. A forty-eight year old woman with 40 per cent third degree burn, treated with electrolytes only during the shock phase and homografts and autografts, on the twenty-third postburn day.

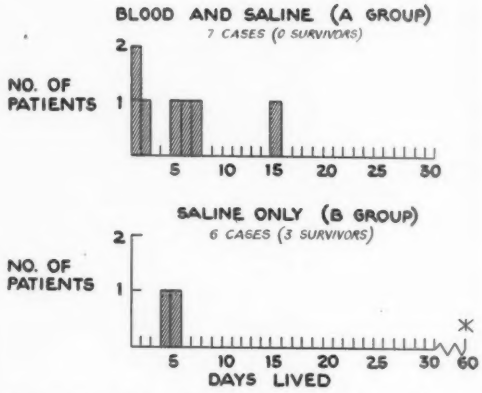


FIG. 6. Comparison of the days lived and type of treatment. A Group patients treated with colloids and electrolytes. B Group, electrolytes only. (One patient died from cardiac arrest two months after burn, during grafting procedure.)

forty-eight hours only. No blood or plasma was given until the fourth day when her hematocrit began to fall. She was given Ringer's lactate solution and 5 per cent dextrose in water through venous cut-downs, at a rate sufficient to maintain her urinary output at approximately 30 cc. per hour. Her rectal temperature rose to 104°F. On the second postburn day, penicillin and streptomycin were administered. The hematocrit, which was 41 per cent on admission, rose rapidly to 52 per cent and then fell to 34 per cent on the fourth day. The first transfusion of whole blood was then given. Her temperature rose to 105°F. at this time. Coagulase positive Staphylococcus aureus was grown on two separate blood cultures. S. aureus and Bacterium aerogenes were consistently cultured from the burn sites. The patient's general condition gradually improved after the fourth postburn day and it was possible to discontinue the penicillin and streptomycin on about the tenth postburn day. A very satisfactory eschar had formed by the fifteenth postburn day, but the temperature became consistently elevated again, probably because of the necrotic material under the eschar.

When S. aureus, sensitive to Chloromycetin® and erythromycin, was again grown from a blood culture it was decided to administer large doses of aqueous penicillin, Chloromycetin and erythromycin in preparation for the first surgical debridement which was carried out on the nineteenth postburn day under general anesthesia.

At this time approximately two thirds of the burned areas were covered with homografts obtained from the National Naval Medical Center; the remaining one third of the burn surface was still covered by an adherent eschar. The remaining

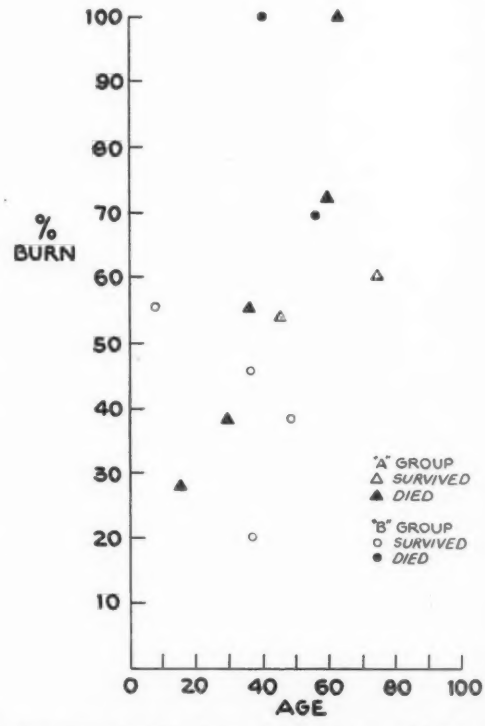


FIG. 7. Comparison of mortality in patients with burns greater than 20 per cent, in Groups A and B.

eschar separated subsequently and was removed at another surgical debridement under general anesthesia on the twenty-third day at which time the remaining burned areas were covered with homografts.

Following the application of these homografts, which covered almost all the burned areas, the patient's fever seemed to be much more easily controlled. However, there were intermittent temperature elevations to 104°F. and the patient subsequently received two courses of Chloromycetin and penicillin therapy.

Following the application of the homografts, the hematocrit gradually fell to a low of 31 per cent and was subsequently restored by whole blood transfusions to 38 per cent.

At the first autografting procedure split thickness skin was taken from the lateral left thigh and was applied to the right axilla and the right groin as well as the burned area of the neck. Approximately 90 per cent of these autografts took very nicely, and the procedure was repeated on the forty-seventh day. At this time thin split thickness grafts were taken from the left flank and the right lateral thigh and were applied to the right arm and a portion of the anterior chest and abdomen. Again, nearly all of the grafts remained viable. This patient was treated entirely by the open technic, with the exception of grafts applied to the burned surfaces of the right arm. (Figs. 4A, B and C.)

COMMENTS

In 1960 a total of thirteen patients with burns involving more than 20 per cent of the body surface were admitted to the San Francisco General Hospital. Of this number, seven patients were treated in the conventional way with blood and saline and received autografts relatively late. Six patients were treated with electrolytes alone during the initial shock phase, and two of the six patients received homografts early in the postburn period. (Fig. 5.) Figure 6 shows the mortality and the date of death of the fatal cases. It is interesting to note that not only were there no survivors in the group treated by the conventional method, but that the time of death tended to be earlier than in the other group. Figure 7 is a comparison of mortality in patients with burns of more than 20 per cent in Groups A and B, indicating also the age of the patients.

SUMMARY

Because of the increasing mortality in burned patients, a revision of the method of treatment of burns has been instituted on the Surgical Service at the San Francisco General Hospital. The initial treatment for burn shock consists of electrolytes without the use of colloids. Oral saline solution is initiated as soon as the patient can tolerate it, which is usually on the first day. Blood is used only during the latent period if a drop in the packed cell volume becomes evident. The prophylactic use of antibiotics has been greatly curtailed. Homografts are used as an early burn dressing.

This method of treatment is compared to the results obtained in the treatment of burns in which the Brooke formula, late autografting and prophylactic antibiotics are used.

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DISCUSSION

Donald T. Hall (Seattle, Wash.): Most treatises on burns indicate considerable problems and frustrations in management and, as Dr. Clark has pointed out, experience has shown that there has been very little, if any, improvement in the overall mortality rate for many years. It seems to be the universal experience that more patients are

saved in the early phases of severe burn therapy by virtue of improved technics and methods of parenteral therapy, only to die in the later phases from infection. Dr. Clark has pointed out the fatalities which are so frequent as a result of infection and my own experience, which has been primarily with children, would certainly bear this out. In commenting upon the exposure method of treatment, I would heartily concur with Artz who has pointed out that the term "open" is rather a misnomer and should rather be "exposure." Certainly a wound which has been treated by the exposure method is covered by a firm, sometimes impervious, eschar under which necrosis and bacterial contamination can and does occur readily. This was brought out in one of our own cases within this past year in which a child treated by the exposure method had a perfectly clean appearing eschar over a considerable portion of the buttocks and both legs without any external clinical evidence of infection, only to die suddenly of extensive metastatic staphylococcal abscesses. There seems to be a tendency on the part of many to believe that infection can be avoided by the exposure method which surely is not true. I think, however, that there is a very good place for both methods of therapy as there are advantages and disadvantages to each, and that a careful selection of method of treatment for each patient is extremely important.

The concept of the avoidance of the use of colloids in the early phases of therapy I look on with rather mixed emotions. Certainly the work of Fogelman and Wilson, Markley and the series as presented by Dr. Clark would indicate that this concept has great merit, or to say the least, is deserving of further consideration and trial. These series as published, however, are small and in my own mind are not conclusive. We have not been aware of any particular pulmonary or renal functional impairment secondary to the use of blood or other colloids, but then there is considerable difference between the group of children with whom we have been working and the older County Hospital aged patients as reported by Dr. Clark. To me, the important consideration here is the possible effect of colloids on potential resistance to infection, whether it be through an effect on the reticuloendothelial system or otherwise. We have used blood early in the course of therapy primarily to curtail the pendulum effect of the secondary fall in hematocrit and hemoglobin after the acute shock phase is over. We have had little trouble in getting patients through the shock phase in those who were not overwhelmingly burned, but again, have been working with a younger group of patients than has Dr. Clark, such that my own great concern centers about that of infection.

In reviewing our own cases over the past fourteen years at the Children's Hospital, we have had what I have considered an admirable mortality rate up until the past year or so when we have lost four children from septicemia, three of the infections due to the pseudomonas organism. For years this organism has been cultured from virtually every third degree burn and we have paid comparatively little attention to it. However, it would appear that more recently either the organism has become much more virulent or there has been a sufficient turbulence in the bacteriological equilibrium secondary to the use of antibiotics that it has been given a more favorable opportunity for invasive action. To me, at the present time, the control of pseudomonas septicemia is the most important and most terrifying facet of burn therapy, even surmounting the shock phase or infection by the coagulase positive staphylococcus. I would heartily agree with Dr. Clark that the use of antibiotics prophylactically is not advisable. It has been our experience also that the use of blood cultures has been of very little help, for by the time these have become positive, the damage has been done and the patient is in a basically irrecoverable phase. The carefully selected use of specific antibiotics for specific organisms does seem indicated, but limited primarily to the treatment for coagulase positive staphylococci or pseudomonas organisms. For this latter, polymyxin has proved helpful and helped us save one child with a severe pseudomonas septicemia. One of the newer drugs, colimycin shows considerable promise. I can only corroborate Dr. Clark's thesis that the basis of successful therapy rests on a meticulous care of the wound with the primary objective of having the wounds grafted as early as possible either by auto- or homografts.

I cannot agree with the concept of early excision and grafting in extensive third degree burns, primarily because there is seldom clear delineation of what is second and what is third degree burn in the patient. Anyone who has attempted to excise a third degree burn of any great extent in a critically ill patient will realize that this is not an innocuous procedure. We have utilized the suggestions of Meeker and Snyder in the use of the electric dermatome to debride third degree burns but, here again, there is sometimes considerable difficulty in delineating deep second from third degree burns and there are oftentimes areas of moist sloughing necrotic skin which do not lend themselves to removal by the dermatome. In the clean, dry eschar the method works admirably.

One other factor that I think is of extreme importance is that of the use of the indwelling urethral catheter. I believe that its use is very dangerous, for in two of the three patients we lost from pseudomonas septicemia, the pseudomonas organism was cultured from the urine at least a week prior to the time that any positive blood culture was obtained. The urethral mucosa is an extremely

absorptive organ and the introduction of organisms into the blood stream through this route is rapid if a catheter is left in for any appreciable time. We believe that if a catheter is required for more than twenty-four hours that it should be placed suprapubically, which we consider a much less radical procedure than placing it through the urethra. I would like to emphasize again the points stressed by Dr. Clark for I think they are so important: namely, the individualization of cases insofar as method of therapy is concerned; the judicious and cautious use of antibiotics for specific organisms; grafting of wounds at the earliest possible time with a more liberal use of homografts. Cadaver grafts work admirably in this situation and their use should be more widely accepted.

CARLTON MATHEWSON, JR. (San Francisco, Calif.): I would like to say a word in defense of Dr. Clark. He has been interested in this perplexing problem for quite some time, but all of his attention has been focused on our city and county hospital. And, as is so often the case, undue criticism has been directed toward him because of the high mortality and high morbidity among his patients. There has also been criticism with regard to our management of bleeding ulcers in that hospital and the high mortality and high morbidity resulting from this later condition.

I think it is important to point out that it is difficult to compare statistics of management in various institutions. The material in one institution is often not comparable to that in another. One should be impressed with the high percentage of alcoholics included in this series. This is true. Most of the burned adults that are brought to this hospital are not only alcoholics but are usually anesthetic from acute alcoholism. They have been alcoholic for days or weeks; they are filthy and covered with bacteria when they come in. Our initial problem has not only been one of electrolyte balance but usually the management of an acute pulmonary status associated with severe alcoholism. The problem of handling the infection in the later phase is frequently complicated by delirium tremens!

I think Dr. Clark should be congratulated on tackling this problem under almost insurmountable obstacles.

ALBERT G. CLARK (closing): We have had a little barrage at times, but it is true that we are dealing with the worst possible candidates for recovery from burns.

I think that one thing we did not cover, but which is most important, particularly in the older patients, is that in any major burn, say 40 per cent and up, a tracheotomy should be strongly considered. We haven't considered it in children. As Dr. Hall has said, we don't see pulmonary edema in these youngsters so often. The older patients do die from it.

I agree with Dr. Hall regarding the use of the catheter. I think the infection may first show itself in the urine.

Experimentation as an Aid in Management of Esophageal Disorders

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POOR results in surgery for benign esophageal disorders often stem from an inability to make an accurate diagnosis. The inaccessibility of the esophagus and the absence in the past of instruments for precise mensuration of esophageal activity have hindered objective evaluation of the patient with an esophageal lesion. To meet the need for greater accuracy in evaluation of esophageal disease, we are utilizing a method of simultaneous measurement of the intraluminal pressure and pH in the esophagus, stomach and the gastroesophageal junction.

The details of the materials and methods used in these experiments have been published elsewhere [1–3]. Briefly, a sensing device consisting of a Beckman pH electrode to which is attached an open-ended, water-filled polyethylene tube is passed transnasally into the stomach. The pH electrode is attached to a Beckman pH meter which, in turn, is attached to a recording device which allows continuous recording of the pH to within 0.1 of a pH unit. The polyethylene tube is attached to a transducer and then to a recording device which allows for continuous measurement of pressure. The pH circuit is completed by placing the reference electrode in the patient's mouth. For measurement of pressures at two or more levels in the esophagus an additional polyethylene tube is attached to the sensing device so that the open end of the second tube is 15 cm. from the end of the sensing device. For measurement of pressures at two or more levels, or for measurement of simultaneous gastric and esophageal pressures, a Grass Model No. 5 polygraph, which is a multichanneled recording device, is utilized. The sensing device consisting of the electrode and polyethylene tube is no larger than a No. 14 Levin tube. It is calibrated in centimeters and after being placed transnasally into the stomach it is drawn cephalad at measured intervals. The type of tracing obtained by this method is shown in Figure 1.

In the normal subject, when the sensing device is placed in the stomach, a slightly positive pressure is obtained and a pH level between 1 and 3 is noted. As the sensing device is drawn cephalad to a point between 40 to 45 cm. from the nares, a pressure inversion point is encountered at which the positive intragastric pressure changes to a negative intraesophageal pressure. In conjunction with this pressure inversion point, usually preceding it, there is a high pressure zone which demonstrates a pressure higher than that in the normal stomach under resting conditions. This high pressure zone extends, roughly, from 1 to 2 cm. along the terminal esophagus. Fluoroscopically this high pressure zone corresponds closely with the esophageal vestibule, or the so-called terminal esophageal sphincter, and is a constant finding in all normal persons. When the sensing device is drawn above the pressure inversion point, the negative intrathoracic pressure appears. As the sensing device is drawn across the high pressure zone the pH changes abruptly, from levels well within the peptic range, around 1 to 3, to a level around 6 in the esophagus. This has been a remarkably consistent finding in all twenty normal subjects studied. Efforts to produce reflux across the high pressure zone in the normal subject in the supine position have included the performance, by the subject, of the Mueller, Valsalva, reverse Valsalva maneuvers, coughing, simulated hiccoughs or singultus, and many other forceful

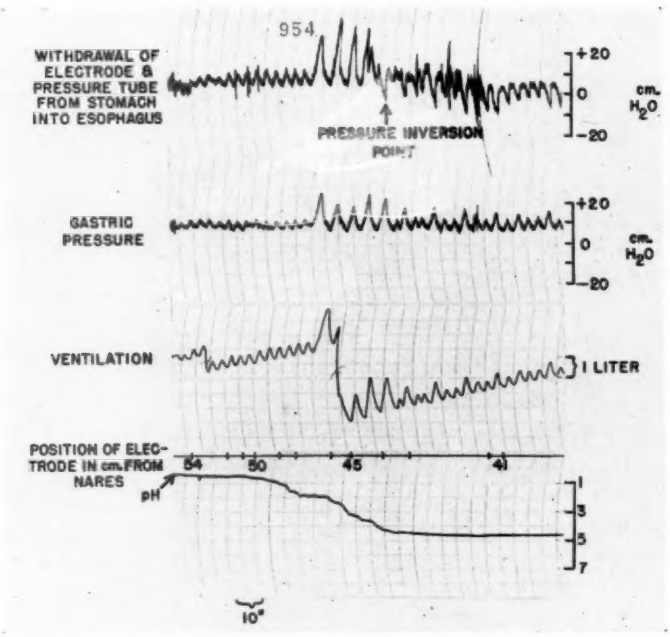


FIG. 1. W. G., April 26, 1960. pH and pressure tracing on normal subject. Note the definite pressure inversion point (P.I.P.) at which the positive intragastric pressure changes to negative intrathoracic pressure. The pressure inversion point is preceded by a high pressure zone where the pressure is higher than the intragastric pressure. The pH changes from a level below 1 to a level near 5 at the high pressure zone.

respiratory maneuvers. In all normal subjects these maneuvers failed to produce reflux. Rarely a normal subject will reflux spontaneously following belching or over distention of the stomach by swallowed air or fluid, or if a polyethylene tube is placed through the gastroesophageal junction into the stomach. Such an occurrence is depicted in Figure 2, which shows reflux confirmed by a drop in pH from a level around 6 to a level around 3. Whenever reflux occurs in the normal subject a powerful swallow wave appears on the esophageal pressure tracing. This wave has been measured as high as 200 cm. of water and is the most powerful contraction we have recorded under the conditions of these experiments. This wave promptly cleanses the lower esophagus of the acid and returns the pH to a level well above the peptic range, as depicted in the tracing. This remarkable cleansing wave, along with the high pressure zone, probably represents the most important barrier to reflux. These studies indicate that the normal gastroesophageal junction is a remarkably competent barrier to the reflux of gastric juice. Simultaneous pH and pressure studies have been made on over 200 subjects, including normals and patients with a variety of esophageal disorders. The most common disorder studied has been hiatus hernia with and without esophagitis. These studies have been valuable in differentiating symptoms caused by regurgitation with or without hiatus hernia, and symptoms related to cardiac, biliary and other abnormalities.

The cause of peptic esophagitis remains unsettled. The most prevalent theory holds that it is due to reflux of acid peptic juice into the esophagus, producing peptic activity in the terminal esophagus. This concept has been questioned because of the lack of objective measurement of reflux. Also, temporary reflux can occasionally be demonstrated in the normal person under the fluoroscope in the Trendelenburg position. Furthermore, esophagitis has been found in association with achlorhydria. Another fact which counters the acid peptic

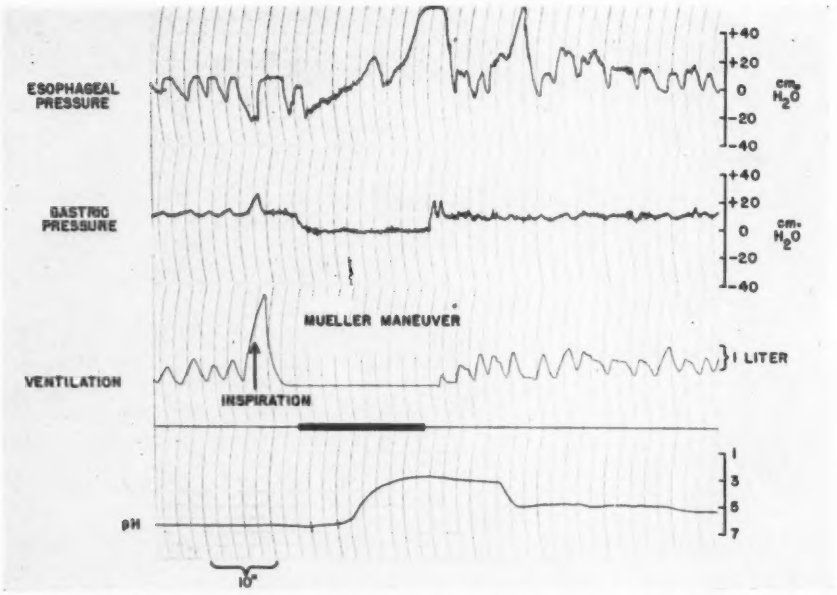


FIG. 2. K. C., May 8, 1960. Four channel tracing on normal subject with polyethylene tube through the sphincter into the stomach. Reflux is evidenced by the change in pH (lower line) in response to a Mueller maneuver. Note the forceful contraction wave developing in the esophagus in response to acid, and the prompt reversion of the pH to a level above the peptic range, following this powerful swallow wave.

origin of esophagitis is the demonstration of submucosal rather than mucosal inflammatory changes in certain cases of esophagitis.

More recent evidence, however, indicates that repeated or prolonged acid peptic bathing of the esophageal mucosa, known to have poor intrinsic protection against peptic digestion [4], is the prime mechanism producing esophagitis. The evidence favoring regurgitation of acid peptic juice as the cause of esophagitis can be listed as follows: Esophagitis occurs exclusively in the lower third of the esophagus. It is a complication of operations which destroy the gastroesophageal barrier, such as resection of the cardia or esophagocardiomyotomy of the Heller type. It can be produced in animals by enlarging the hiatus. Further evidence lies in the fact that the acidity of fluid collected by means of an intraesophageal tube during sleep corresponds closely to the presence and degree of esophagitis observed by the endoscope. In patients with proved esophagitis, irrigation of the esophagus with a dilute hydrochloric acid reproduces the pain of which the patient complains.

An alternative view to a purely acid peptic production of esophagitis is found in the concept that acid peptic juice serves as an irritant, producing edema and interference with the vascular supply of the terminal esophagus. In addition, constant irritation by acid peptic juice produces violent contractions of the terminal esophagus, as evidenced by our studies. This continued muscular contraction, with exhaustion of the muscle fibers of the terminal esophagus, coupled with the edema, both interfering with the vascular supply and nutrition of the terminal esophagus, damage the integrity of the esophageal wall, destroying its resistance to peptic activity. This sequence of events is then followed by peptic digestion of the damaged esophageal mucosa. This view can explain the rare patient in whom esophagitis develops in the presence of achlorhydria, or following total gastrectomy in which alkaline juice, rather than an acid secretion, serves as an irritant.

Direct determination of the pH in the esophagus by means of the pH electrode has helped in clarifying this problem, especially with

reference to the detection of reflux. Peptic activity is minimal at a pH below 1. It rises sharply to a peak at pH 2.3 and gradually falls to about 20 per cent at pH 4. At 5, peptic activity is absent [5]. In our material a low esophageal pH in the terminal esophagus has been found almost invariably in patients with esophagitis. One exception to this is a patient under observation who has had a total gastrectomy, with ulceration in the terminal esophagus with alkaline reflux.

A measurement of the pH in the terminal esophagus gives the surgeon an objective determination of the amount of regurgitation in peptic activity occurring in this location. This has been especially helpful in differentiating earlier forms of esophagitis from those conditions which can mimic esophageal disease, especially cardiac and biliary tract disorders.

COMPATIBLE SYMPTOMS WITH NO DEMONSTRABLE HIATUS HERNIA

The clinician frequently encounters patients with symptoms that resemble reflux esophagitis, as well as the pain of angina pectoris, peptic ulcer or biliary colic. In these situations it may be impossible to determine the origin of the symptoms without objective studies. Twelve patients have been studied in whom no demonstrable hiatus hernia was present by conventional x-ray examination but who had symptoms resembling esophagitis. Electrocardiograms in nine of these patients were normal and yet several of them had been told they were suffering from heart disease. During testing in these patients, reflux into the terminal esophagus was demonstrated by a fall in the pH from levels around 6 to as low as a pH of 1. At this point the patient stated that this was the type of pain for which medical advice had been sought. These patients with minimal esophagitis have been placed on a medical regime and are under observation. Without objective studies, these patients present difficult problems in differential diagnosis.

Conversely, we have had the opportunity to study patients who had substernal pain and a demonstrable hiatus hernia, but in whom the pain was bizarre. These patients had pain both in the supine position compatible with reflux esophagitis, and pain on exertion compatible with angina pectoris. The electrocardiogram at rest may be normal. By obtaining a simultaneous electrocardiogram, pH and pressure tracing, it can be demonstrated that the pain which develops in response to reflux in the supine position is different from the pain experienced in the erect position brought on by exertion. With the electrode and pressure tube in place, as well as the electrocardiographic leads, the Master's two step test is performed. A drop in the ST segment of the electrocardiogram, coincident with substernal pain, indicates myocardial ischemia. The absence of reflux in the terminal esophagus, as demonstrated by the pH electrode, rules out reflux as a cause of this type of pain. Thus, a graphic demonstration of the two different types of pain can be elicited. Obviously, operation on this type of patient for hiatus hernia does not answer the patient's entire problem. The relationship of hiatus hernia to angina pectoris has been the center of a great deal of clinical and experimental investigation. This complex subject is being investigated in detail by this method and will form the material of a later report.

SLIDING HIATUS HERNIA

Sliding hiatus hernia with and without esophagitis has been the most common condition studied in this series. The small hiatus hernia represents the most common form. Approximately 210 patients have been operated upon with sliding hiatal hernia. Of these, 140 were classified as small, or arbitrarily containing less than one fourth of the stomach in the thorax, with the hiatal opening admitting less than four fingers at the time of surgery. In this group, again, one encounters difficult diagnostic problems. In a given patient with multiple complaints it is often impossible to ascertain how much of the patient's disability is due to the presence of a small hiatal hernia. A group of patients studied had minimal reflux with hypochlorhydria, with a small hiatus hernia. The major symptoms in these patients were related to angina or biliary tract disorders, rather than to the small hiatal hernia. In this group operation is often disappointing, as simple correction of the hernia does not attack the prime problem for which the patient is seeking relief. Conversely, many patients with a small hiatus hernia with reflux have been treated for peptic ulcer, heart disease or disorder of the biliary tract without a definitive

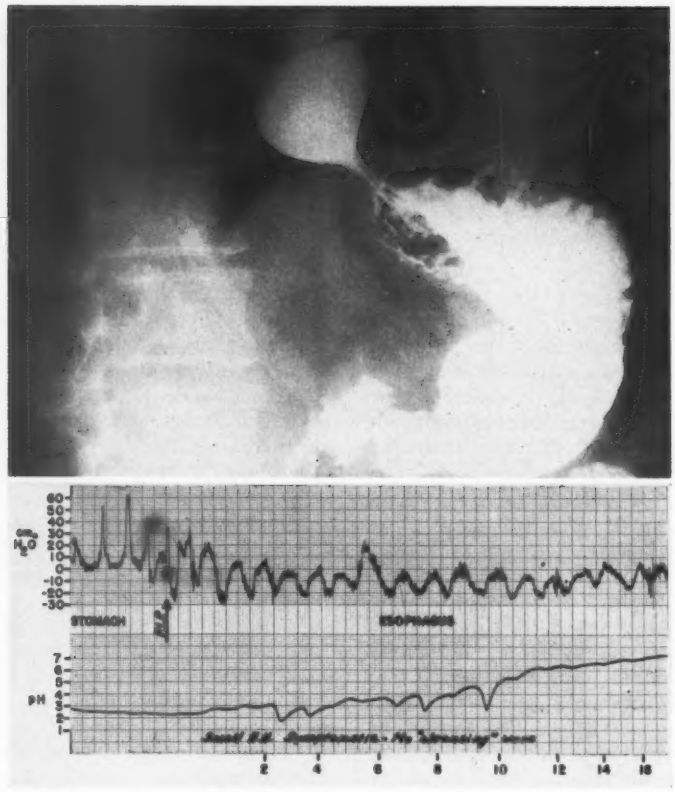


FIG. 3. D. N. Tracing on small hiatus hernia showing evidence of free reflux, influenced by respiration to a level of 10 cm. above the pressure inversion point. Note the absence of swallow waves in response to reflux.

diagnosis. During testing of patients in this group, it can be ascertained that the patient is not hypochlorhydric and that definite reflux is occurring. Often the patient's chief complaint can be reproduced during the procedure. A tracing on such a patient, along with the gastrointestinal series, is shown in Figure 3. Note that the pH fails to rise at the pressure inversion point and reaches a level outside the peptic range only after the sensing device is drawn 10 cm. above the pressure inversion point. This patient had free reflux with respiratory maneuvers and was suffering from severe symptoms. Note that in spite of free reflux there is no high pressure wave developed in the esophagus in response to reflux of acid. Moderate esophagitis was confirmed by esophagoscopy. Operation was performed and a postoperative tracing showed a return of the pressure and pH profile to normal. Postoperatively, respiratory maneuvers failed to produce reflux. In effect, the patient's altered physiology had been corrected so that his tracing was indistinguishable from that of a normal subject.

Those sliding hiatal hernias in which one fourth or more of the stomach is dislocated into the thorax we have arbitrarily designated as "large hiatal hernias." All the large hernias, that we have studied, with two exceptions, have had marked symptoms and free reflux. In two patients hypochlorhydria was found, even after Histalog. These two patients had minimal symptoms. pH and pressure studies in the large symptomatic hiatal hernia show that the pH does not rise out of the peptic range until the sensing device has been drawn well up into the esophagus, above the gastric pouch dis-

located into the thorax. Esophagitis has been confirmed in the majority of these patients by esophagoscopy. Following an adequate repair of the large hiatal hernia, the postoperative tracing shows the pH and pressure profile returned to normal. At the present time we have studied more than fifty patients with large hiatal hernia.

PARAESOPHAGEAL HERNIA

In contrast to the sliding hiatal hernias, which are relatively common, parahiatal hernias are uncommon. These hernias may reach enormous size, with the entire stomach and first portion of the duodenum dislocated into the thorax. We have encountered ten of these hernias in our series which represents, now, over 210 patients operated upon. Of the ten, physiologic studies have been made in six paraesophageal hernias of significant size. An example of this type of hernia is shown in Figure 4. Patients in this group may suffer severe symptoms due to incarceration of the stomach in the chest. In the patient depicted the entire stomach and the first portion of the duodenum were incarcerated in the thorax. Symptoms have ranged from severe crushing substernal pain with hemorrhage, to marked dysphagia. Bleeding has been encountered in four instances of large paraesophageal hernia. We have studied six of these patients and in none have we found reflux to be the cause of symptoms. pH and pressure studies confirm what can be suspected from the x-ray findings, namely that there is a competent terminal esophagus with little or no tendency to reflux. Negative intrathoracic pressure is encountered while the electrode is in the thoracic stomach and the pH at this point is well within the peptic range. The electrode may then pass into the duodenum, at which point it crosses the pressure inversion point and enters the abdomen. These tracings may be confusing unless correlated with the x-ray findings in these large hernias. At operation upon these patients the esophagus is found to be firmly fixed in its normal position, with a well defined phrenoesophageal membrane. Reduction of the hernia from the thorax into the abdomen and closure of the large paraesophageal opening corrects the altered physiology in parahiatal hernia. The postoperative tracings show a return of function to normal if the repair is adequate.

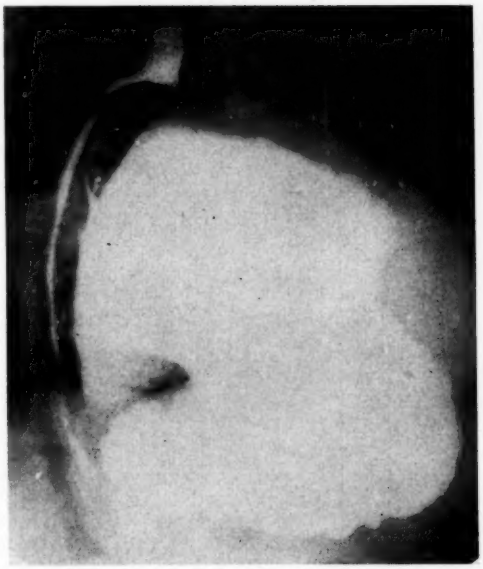


FIG. 4. Barium roentgenogram on subject with parahiatal hernia, including all of stomach and first portion of the duodenum in the thorax. The esophagus extends well below the diaphragm and is fixed in this position by a well developed membrane. Tracing on this subject demonstrated no reflux and a normal gastroesophageal junction.

SURGICAL REPAIR

The type of repair that has been used in both the sliding and parahiatal hernia is depicted in Figure 5. This repair consists of reduction of the hernia, excision of the hernia sac, approximation of the leaves of the right crus of the diaphragm, reconstruction of the gastroesophageal angle, resuturing of the phrenoesophageal membrane and suturing of the fundus of the stomach to the under surface of the diaphragm. Figure 5 shows complete correction of the pH and pressure relationships to normal. Note the rise in pH which occurs before the sensing device reaches the high pressure zone, indicating that the reconstructed gastroesophageal angle may well act as a barrier to acid below the diaphragm. This simple mechanical repair will suffice in the vast majority of early hiatal hernias. In those patients with marked ulcer diathesis in whom there is a low pH in the range of 1 to 2 in the stomach and in whom the terminal esophagus has lost its ability to contract in response to reflux of acid, it is doubtful that simple mechanical correction by any presently devised means will prevent sub-

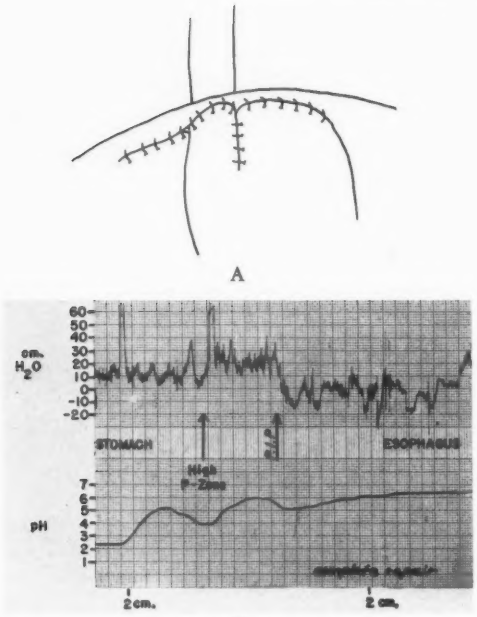


FIG. 5. W. M. Postoperative tracing on a patient with a complete repair. High pressure zone, pressure inversion point (P.I.P.) and conversion of pH have been restored to normal.

sequent reflux. This is particularly true for the supine position as when the patient is relaxed during sleep. The tracing in Figure 5 shows a distinct pressure inversion point and a definite high pressure zone. In these patients with adequate repair all respiratory maneuvers failed to produce reflux.

In contrast to an adequate repair, simple closure of the hiatus has been demonstrated by these studies to be an inadequate operation. Figure 6 shows a postoperative tracing on a patient who had simple closure of the hiatus seven years ago, before additional reconstructing sutures were generally used in this operation. Free reflux is demonstrated by a fall in the pH to levels around 1 to 2, as high as 7 cm. above the pressure inversion point. This patient was having severe symptoms in spite of the fact that he had been operated upon. Numerous postoperative studies, such as this, present convincing evidence that simple closure of the hiatus will not correct the tendency to reflux in a sufficient number of patients to be considered an adequate surgical operation. For long standing esophagitis, reconstruction sutures and vagotomy and pyloroplasty have given excellent results up to five years.

RECURRENT HERNIA

These studies have been found to be most valuable in detecting the presence of recurrent hernia. Figure 7 shows a tracing on a patient who had previously had an adequate repair with complete relief of symptoms, but who attempted to lift a 400 pound weight six months after operation. He felt a sudden pain in the chest, following which recurring symptoms of esophagitis developed. Gastrointestinal series showed no evidence of hiatus hernia and no reflux in the Trendelenburg position, but pH

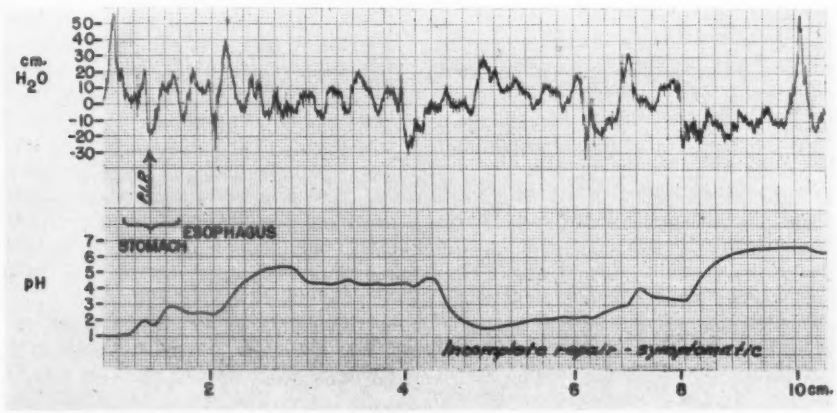


FIG. 6. F. L. Tracing following an incomplete repair shows persistent reflux to 8 cm. above the pressure inversion point. Substernal burning occurred during testing.

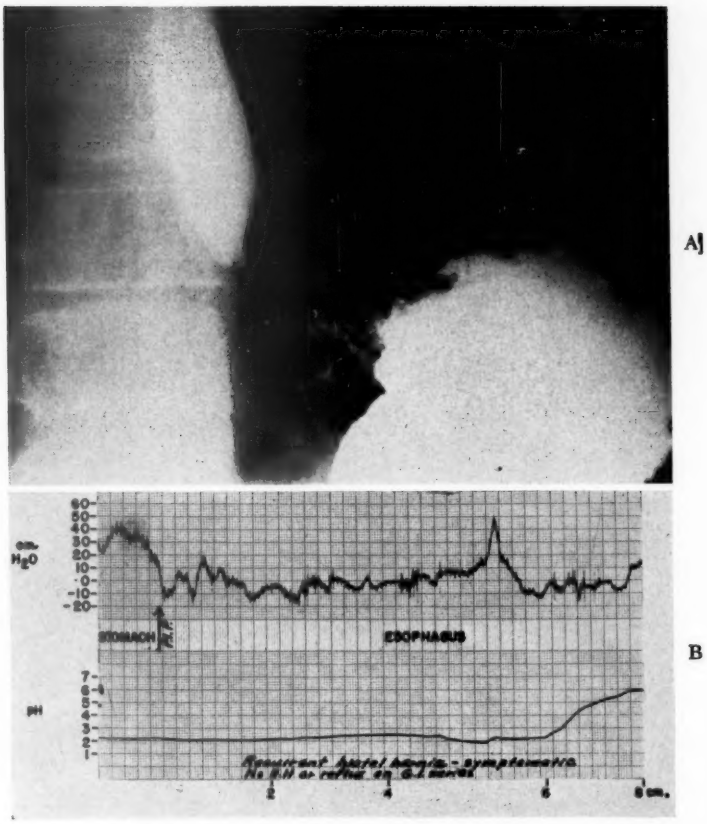


FIG. 7. E. M. Tracing on symptomatic recurrent hiatal hernia gastrointestinal series shows no evidence of recurrent hernia and fluoroscopy showed no reflux. The tracing shows reflux to 6 cm. above the pressure inversion point. Symptoms occurred during testing.

and pressure studies showed obvious reflux up to 6 cm. above the pressure inversion point. Note on the tracing that the pH fails to rise until the sensing device has been pulled well above 6 to 7 cm. above the pressure inversion point. This patient was repaired again, and a vagotomy and pyloroplasty were added to the repair. He has been free of symptoms since surgery.

STENOSING ESOPHAGITIS

In previous reports we have outlined our experience with stenosing esophagitis [1,2]. In four patients operated upon, we have encountered two varieties of this severe form of esophagitis. We have studied an additional eight patients in this group. The two forms are represented by the long, narrowed, stenotic segment on the one hand, and the discrete marginal ulceration with stenosis on the other. A typical study in such a patient is shown in Figure 8. In this patient with almost complete obstruction of the esophagus, severe burning pain occurred in the supine position. The patient had hemorrhaged on repeated occasions and eventually became completely obstructed. An esophagoscopy revealed advanced ulceration of the esophagogastric junction. The tracing demonstrates dramatically the devastating effect of the supine position on the sensitive ulcerated esophagus. Note in the tracing on the left that while the patient is in the sitting position there is relatively little activity in the esophagus and the pH is at a resting level be-

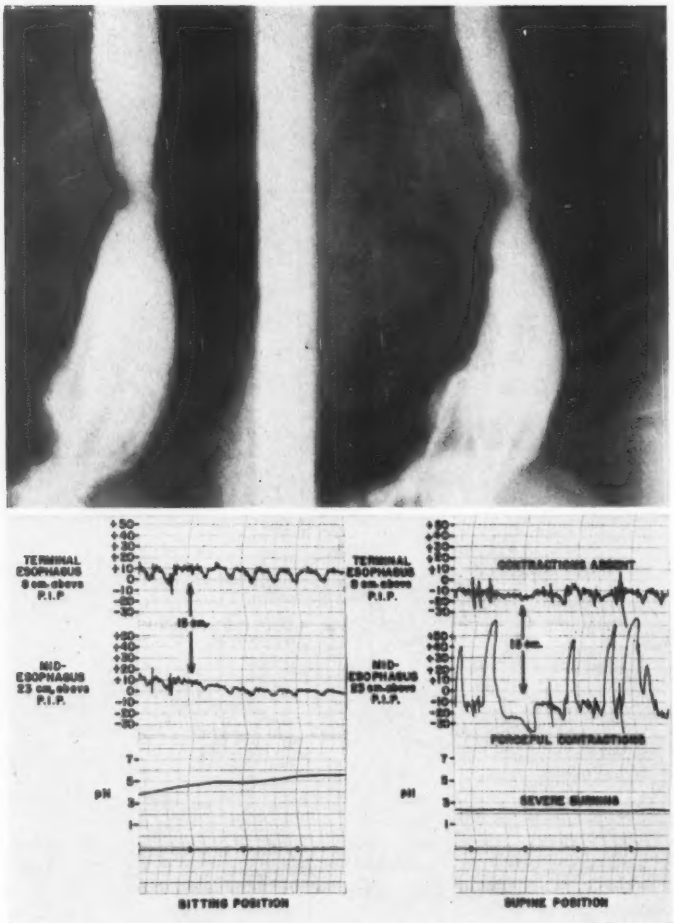
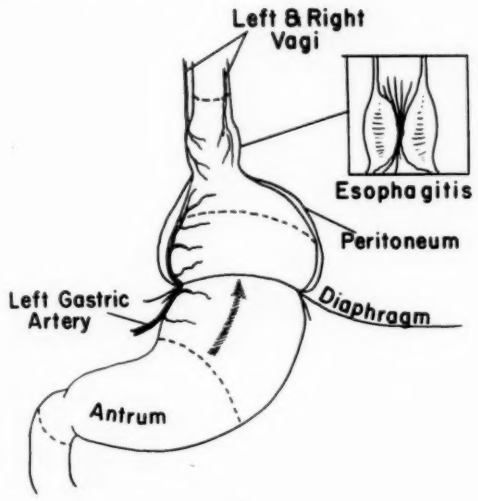


FIG. 8. C. C. J., February 11, 1961. Hiatal hernia and stenosing esophagitis. Four channel tracing on patient with severe stenosing esophagitis illustrating profound effect of the supine position which produces free reflux, followed by powerful contractions in the midesophagus, with no activity in the diseased distal esophagus. Severe burning pain occurred during testing.

tween 4 and 6. In this experiment a pressure tube was placed in the terminal esophagus 8 cm. above the pressure inversion point and a second pressure tube was placed 15 cm. above the first. The pH electrode was in the terminal esophagus. With all sensing devices fixed in the same location, the patient was placed in the supine position. Upon assuming the supine position, free reflux all the way into the pharynx was noted, with a drop in the pH to a level just above 2. Violent contractions of the midportion of the esophagus, with extreme high pressure waves were demonstrated. In the terminal esophagus there was little or no contraction, indicating that the markedly diseased and fibrotic lower esophagus was incapable of responding to reflux of markedly acid fluid and that the mid-esophagus, where esophagitis is not so advanced responds with forceful contractions in an apparent effort to cleanse the esophagus of the irritating gastric contents. Since the terminal esophagus is incapable of contraction, it is obvious that it has virtually no defense against free reflux in the supine position. It is this

continued bathing of the damaged esophagus during sleep which forces these patients to assume an almost erect position in order to avoid pain. In those patients operated upon for severe stenosing esophagitis, we have utilized a modification of the procedure described by Ellis. There has been no operative mortality in this group. One patient died subsequently of pneumonia at the age of seventy-four. In this patient operation was mandatory because of complete obstruction and hemorrhage. The operative procedure is depicted, both at operation and by diagram in Figure 9. The vagotomized and antrectomized pouch is sutured to the esophagus after the damaged terminal esophagus has been removed. The antrum of the stomach is removed and a gastrojejunostomy is performed. We have added to this a jejunojejunostomy, which increases the food reservoir and serves to prevent alkaline secretion from refluxing into the stomach pouch and thence into the esophagus.

Postoperative studies on these patients show the pH in the pouch to be in the range of 6 to 7 for the most part. However, by carefully moving the sensing device, a small central area in which the pH is around 2 has been found on one of these patients. Three patients are relatively free of symptoms, however, and esophagoscopy shows no evidence of esophagitis. It is obvious that surgery should be instituted in these patients long before severe stenosis with ulceration and shortening occurs. A large resectional procedure can be avoided by earlier operation. Patients operated upon by this technic have remained free of symptoms and in an excellent nutritional state up to two and one-half years following surgery.



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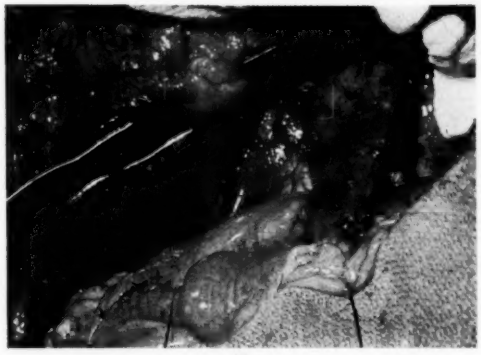

B

FIG. 9. Modified Ellis operation utilized for severe stenosing esophagitis.

ACHALASIA

Code et al. [6], Ingelfinger [7], Templeton [8], and others have accurately demonstrated that achalasia, or cardiospasm, is a neuromuscular disorder characterized by absence of true swallow waves in the body of the esophagus, uncoordinated spasm of the lower esophagus and failure of the gastroesophageal junction to open in response to swallow waves. pH and pressure studies in our laboratory indicate that reflux does not play a part in the symptomatology of achalasia. We have further confirmed in our laboratory the findings of Ingelfinger, Code, and others, that there is an abnormal response to injection of methacholine chloride (Mecholyl®) in the presence of true achalasia. Following the administration of 10 mg. of Mecholyl intramuscularly, there is a marked rise in the intraluminal pressure in the terminal esophagus, with spasmodic contraction waves, followed by severe pain and retching on the part of the patient. This phenomenon does not occur in the normal person. This test has been demonstrated to be quite sensitive and serves as an excellent means of differentiating early states of achalasia from scleroderma and psychosomatic esophageal disorders.

In our experience the majority of patients with achalasia will respond adequately to

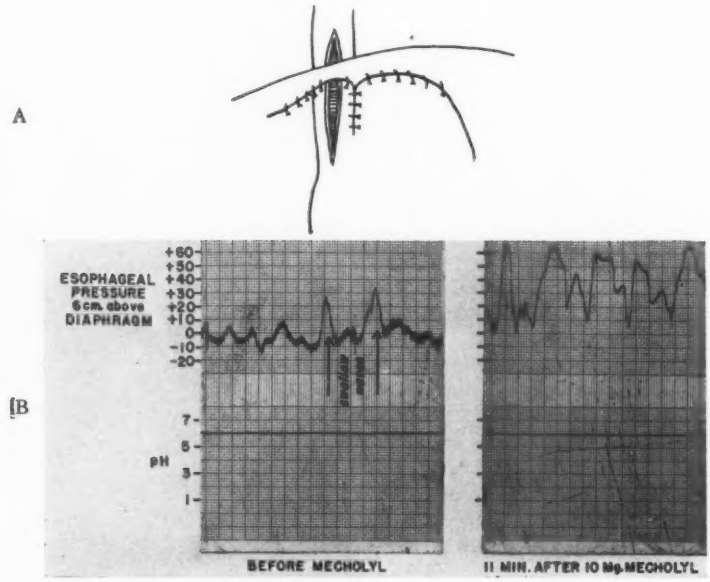

FIG. 10. Tracing taken following Heller operation for achalasia, showing continued abnormal response to Mecholyl. Note the absence of reflux, as demonstrated by the pH following an adequate modified Heller operation.

dilatation. In those patients who have failed to respond to conservative measures, we have used the Heller operation. Studies on four patients who have had the Heller operation indicate that while this operation relieves the obstruction at the gastroesophageal junction, it does not alter the abnormal response to Mecholyl, indicating that the uncoordinated spasm of the terminal esophagus is still present. Figure 10 shows a postoperative tracing on a patient with a Heller operation which has been modified. The modifications depicted are reconstruction of the gastroesophageal angle, suturing of the fundus of the stomach to the under surface of the diaphragm, and reapproximation of the phrenoesophageal ligament. These measures have been instituted to offset the prime objection to the Heller operation, namely, postoperative reflux following division of the gastroesophageal junction. In the patients who have been studied with this type of repair, there has been no evidence of reflux, as shown in Figure 10. Even with forced respiratory maneuvers, the pH remains at a level around 6 in the terminal esophagus. Patients with this type of repair have remained free of symptoms up to two years following surgery. In contrast to this, two patients who had a transthoracic Heller operation without reconstruction of the gastroesophageal angle, fixation of the stomach and repair of the hernia, have been studied and found to have marked reflux in the terminal esophagus. Both of these patients have severe symptoms related to terminal esophagitis.

DIFFUSE SPASM OF THE ESOPHAGUS

Diffuse spasm of the esophagus has been clearly appreciated only recently, following the work of Code [6], Moresch and Camp [9]. We have confirmed in our laboratory that diffuse spasm consists of a violent, uncoordinated, simultaneous contraction of the entire esophagus in response to deglutition. The gastroesophageal sphincter, in contrast to the findings in achalasia, relaxes in response to deglutition. We have further shown that during this state of relaxation of the gastroesophageal sphincter regurgitation into the terminal esophagus may occur. This is demonstrated clearly in Figure 11. The response to Mecholyl is not constant in diffuse spasm, but the patient depicted in Figure 11 showed a violent response to 10 mg. of

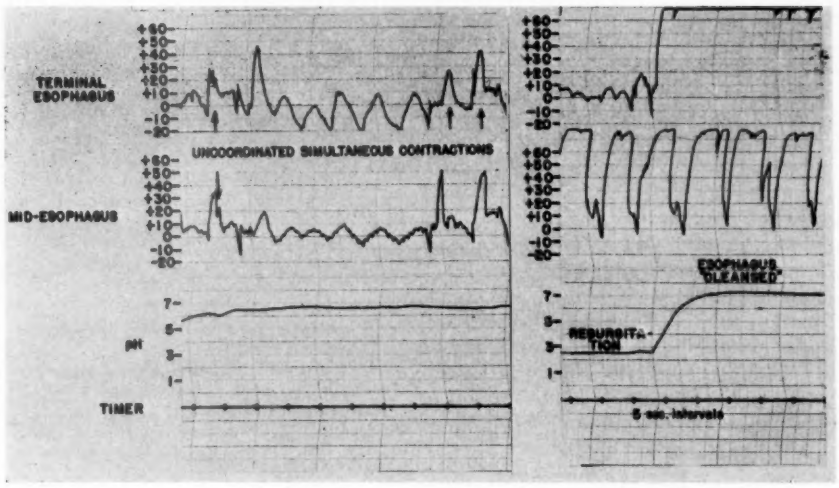

FIG. 11. Mrs. N., February 4, 1961. Four channel tracing on patient with diffuse spasm of the esophagus. Note simultaneous contraction of mid- and terminal esophagus, and absence of progressive swallow waves. A, before Mecholyl. B, abnormal response to Mecholyl is depicted. These powerful contraction waves caused severe pain and cleansed the esophagus of acid, as shown on the pH reading.

Mecholyl injected intramuscularly. In Figure 11 the left hand portion of the tracing shows the simultaneous swallow waves occurring both in the mid- and terminal esophagus, with no progression of a well defined peristaltic wave down the esophagus, as is seen in normal tracings. In the right hand section of the tracing, regurgitation with a fall in the pH to a level of 2.5 is shown, along with the violent contractions in response to Mecholyl. Following these contractions, which developed pressure in the esophagus well in excess of 60 cm. of water, the esophagus was cleansed of acid and the pH suddenly reverted to a level around 6. The exact role of reflux in this condition is not clear. It would appear from these studies that the principle defect is the severe uncoordinated contraction involving the entire esophagus simultaneously.

Clinically, this condition is characterized by severe substernal pain and great difficulty in swallowing solid food. Often attempts at swallowing liquids are followed by violent contractions of the esophagus, with spill over into the trachea, and coughing. During the clear-cut demonstration of reflux in Figure 11, the patient experienced severe substernal pain. It cannot be stated whether this pain was primarily due to gastric juice in the terminal esophagus or to the violent spasmodic contractions. Perhaps both factors contribute to the pain. Further studies on this condition are in progress. It is obvious from these findings, however, that a limited Heller operation will not correct diffuse spasm of the esophagus. We have not, as yet, operated upon the patients whom we have under observation, but the reported good results with the long Heller, as performed by Ellis, appears to be a logical solution to this problem, as long as the tendency to reflux in the terminal esophagus is offset.

SUMMARY

Simultaneous pressure and pH studies have been performed in over 200 subjects, with a wide variety of esophageal disorders, and in twenty normal subjects. From these studies the pH and pressure profiles have been clearly depicted in both health and disease. Combined studies with two pressure tubes in the esophagus have deomonstrated the progression of swallow waves in the normal subject, and the failure of the progression of swallow waves into the terminal esophagus in the patient with advanced esophagitis. Combined studies with a pressure tube placed in the esophagus and one in the stomach has allowed a measurement of the gradients across the gastroesophageal

junction. The influence of these gradients in producing reflux indicates that the conventional maneuvers, such as the Mueller and Valsalva which are employed by the roentgenologist in an effort to produce reflux, often close the esophagus tightly and prevent reflux in spite of a large pressure gradient across the gastroesophageal junction. The most potent maneuvers that produce the highest pressure gradients across the junction have been inspiratory sniffing and simulated hiccoughs, or singultus. These have produced pressure gradients as high as 200 cm. of water across the sphincter and are the best means of producing reflux. In a final analysis, however, the most frequent condition under which we were able to demonstrate reflux has been the supine position with the patient relaxed.

These studies have been standardized to the point where they are an integral part of the evaluation of the patient with esophageal disease. They are particularly helpful in detecting the early stages of esophagitis, achalasia, diffuse spasm, scleroderma, as well as other benign esophageal disorders. They have been useful in delineating the underlying mechanisms of esophageal disease. Pre- and postoperative studies on unusual conditions such as Schatzki's ring and high gastric diverticula have been illuminating.

With these technics the surgeon has an objective means of determining the presence of early derangement of the esophagus preoperatively and thereby is in a better position to avoid many of the poor results in surgery which stem from an inaccurate diagnosis. In addition, postoperative studies and posttreatment studies serve to define objectively the effect of therapy. Our studies indicate that simple closure of the hiatus is an inadequate operation for reflux esophagitis.

These studies also point out that reconstructing sutures should be applied in conjunction with the Heller operation in order to prevent reflux following this procedure. These studies have been helpful in differentiating the pain of angina pectoris from that of reflux esophagitis and in delineating reflux in those subjects in whom no demonstrable hernia or reflux could be demonstrated by conventional roentgenographic technics. Further studies to define the influence of vagotomy and other ancillary procedures employed in esophageal disease are in progress.

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DISCUSSION

Carleton Mathewson, Jr. (San Francisco, Calif.): Aside from congenital deformities, acute perforation and neoplasms, the lesions of the esophagus of greatest concern to the surgeon are those associated with peptic esophagitis. While it is known that there is a physiologic sphincter mechanism at the cardioesophageal junction which under normal circumstances prevents the regurgitation of gastric contents into the lower esophagus, the true nature of the sphincter is not known. It is believed by some that this is an intrinsic mechanism, completely related to nervous and muscular mechanisms within the wall of the esophagus; while others are equally convinced that it is an extrinsic mechanism controlled by the crura and other musculature in the diaphragm. Still others have suggested a combination or inter-relationship of these two. All have agreed that an incompetent sphincter in this region allows a reflux of gastric contents into the esophagus with resultant irritation and the development of esophagitis and its sequelae.

Although peptic esophagitis has been recognized as a disease entity since its first description as such by Winkelstein in 1932, only in recent years have surgeons concerned themselves with the early manifestations of the disease and advocated surgical management before ulceration and fibrosis have have led to irreparable stenosis and shortening.

Unfortunately our lack of knowledge of the basic defects in the sphincter mechanism leading to regurgitation has led to many improper and unphysiologic surgical approaches to the problem.

In recent years it has become apparent, mainly by trial and error, that regurgitation occurs when the cardioesophageal junction has been displaced from its normal position below the diaphragm, as is seen in association with a sliding type of hiatus hernia, and can be corrected by replacement of this juncture to its normal position. This observation has led most surgeons to believe that the angle of entrance of the esophagus into the stomach (the so-called "cardioesophageal angle") is the most important factor concerning a competent sphincter.

The recent acquisition of precise instruments to measure pressure gradients and pH values in the stomach and esophagus have now, not only added to our diagnostic armamentarium, but have provided us for the first time with an accurate means of evaluating the operative procedures applied to these conditions. Dr. Hill has demonstrated rather conclusively that simple closure of a hiatal defect around the esophagus does not prevent regurgitation. We are inclined to agree with him and are now studying a group of patients in whom repair has been accomplished by simple reduction of the hernia by traction and fixation of the stomach against the anterior abdominal wall.

Dr. Hill has also been able to demonstrate that paraesophageal hernia, when symptomatic, is not due to regurgitation. We have now seen a few patients who have been cured of their symptoms of esophagitis by repair of a hiatus hernia only to develop an entirely new symptom complex resulting from herniation of the stomach through the counter incision made in the diaphragm at the time of the repair. We believe that this maneuver is dangerous and an unnecessary part of the surgical repair.

We have only recently commenced studies similar to those described by Dr. Hill this morning and are convinced that they will aid us immeasurably in the future in the recognition and management of diseases of the esophagus and should help clarify many of the perplexing problems that confront us at the present time.

As has been indicated by Dr. Hill, simple restoration of the "cardioesophageal angle" is not a cure-all. In many incidents it is necessary to undertake accompaning procedures to control acid secretion and to promote prompt gastric emptying. Certainly, when peptic ulceration in the stomach or duodenum are associated with hiatus hernia, and they frequently are, both conditions must be corrected for an effective result.

LUCIUS D. HILL (closing): I have nothing to add except to say that Dr. Mathewson's contributions in this area are well known, and it is a privilege to have him discuss this paper.

Experimental Studies in Cryobiology

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From the Department of Surgery, University of Oregon Medical School, Portland, Oregon. This investigation was supported by Public Health Service Research Grants C-4780 (C2) from the National Cancer Institute and RG-6483 (C1) from the Research Grants Branch, Division of General Medical Sciences.

CRYOBIOLOGY [1] is the study of the effects of cold on living organisms. The effects of extreme cold on isolated cells, the use of low temperatures for preservation of whole organs, the effect of prolonged suspended animation on entire animals and the survival of skin grafts and growth of tumors in such animals have been under study in our laboratory during the past three years. Cells and thin slices of tissue will survive at low temperatures but many problems must be solved before normal function can be restored after subjecting a whole organ or an entire organism to extremes of cold.

SURVIVAL OF FROZEN CELLS AND TISSUES

Initially, observations were undertaken on the resistance of tissues, particularly human tissues, to temperatures approaching absolute zero, −273.16°C. (Fig. 1.)

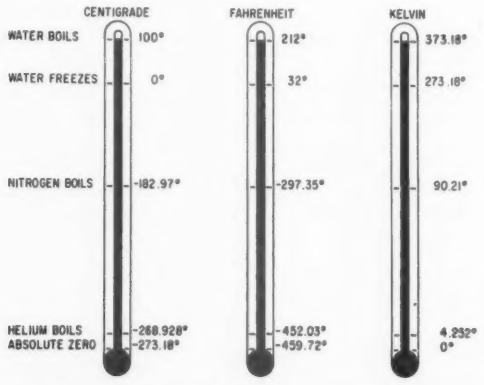

FIG. 1. Comparative low temperature chart.

Technic. Human conjunctival cells, saturated with 6 per cent glycerol solution, human spermatozoa without glycerol, human spermatozoa pretreated with one part glycerol to nine parts semen, the Coksackie virus without glycerol, and dog and rabbit skin previously immersed in 15 per cent glycerol-saline solution, were frozen to −272.2°C. After this low temperature had been maintained for thirty minutes, the material was thawed in a 26°C. water bath and subsequently tested for viability.

All tissues were enclosed in sealed glass ampoules and placed on a specially constructed brass plate under which liquid nitrogen was circulated. The ampoules were covered by glass wool for insulation and the plate cooled by circulating the liquid nitrogen. When the temperature of the ampoules reached −180°C, over a two hour period, the glass containers were freed from the plate and placed into a Dewar flask with a side arm containing liquid helium.

Freeing of the ampoules from the plate was facilitated by inserting a layer of grain alcohol between them and the plate prior to freezing. The vapor pressure was then lowered to 80μ Hg, equivalent to −272.2°C., by applying a vacuum pump to the side arm of the Dewar flask holding the liquid helium. After a half hour at this temperature, the vacuum was released and the removed ampoules thawed in a 26°C. water bath.

The human conjunctival cells were tested for viability in tissue culture by a method described by Chang [2]. Motility was used for the criterion of spermatozoa survival. Viability of the Coksackie virus was demonstrated by culture. Autogenous transplantation of rabbit and dog skin was the standard for studying the survival of these tissues.

Results. Human conjunctival cells presatured with 6 per cent glycerol solution and

frozen to within one degree of absolute zero, will survive and continue to proliferate in tissue culture after thawing. The growth appeared heavy but quantitative studies were not made. Ten per cent of human spermatozoa without added glycerol will be motile when thawed from −272.2°C. When one part glycerol to nine parts semen solution was added before freezing, 60 per cent exhibited motility after thawing. The Coksackie virus will survive −272.2°C. without prior glycerol saturation. Autogenous rabbit and dog skin, pretreated with glycerol will "take" when transplanted orthotopically, two of two segments of rabbit skin and three of three pieces of dog skin remained viable.

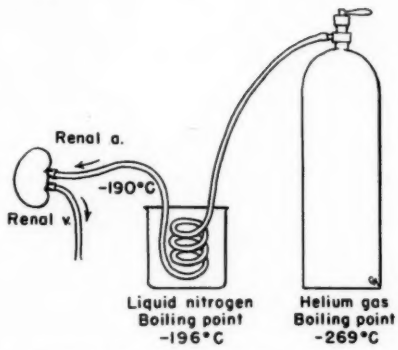

FIG. 2. Technic of freezing a kidney by way of its vasculature.

FREEZING OF WHOLE ORGANS

Encouraged by the demonstration that cells and then thin slices of tissue will withstand temperatures of −272.2°C., an attempt was made to freeze entire organs. An entire kidney frozen to low temperatures and thawed by conventional means, in addition to functional loss, exhibits gross and microscopic evidence of cracking.

Technic. Two technics have been described by us to obviate fragmentation of the whole kidney, frozen as low as one degree above absolute zero. In both, the right kidney of a dog was removed with the animal under nembutal anesthesia and the vasculature flushed with dilute heparin-saline solution. A thermocouple was inserted into the kidney substance and freezing to within one degree of absolute zero was accomplished by one of the following methods:

1. Helium gas which boils at −269°C. was circulated through a copper coil immersed in liquid nitrogen entering the renal artery at −190°C. under 3 pounds pressure through a metal cannula. (Fig. 2.) The gas then emerged via the renal vein. It required two and a half hours for the temperature in the center of the kidney to reach −180°C. The kidney was positioned in a Dewar flask holding liquid helium and the vapor pressure droped to 80μ Hg or −272.2°C. The kidney was then thawed to 4°C. over a half hour period by helium gas at room temperature passed into the renal artery.

2. The kidney was placed on the upper surface of a brass plate, 1¾ inches thick and 4 inches in diameter into which a copper coil had been built. One end of the coil was seated in a small Dewar flask containing liquid nitrogen and the other end attached to an ordinary laboratory vacuum pump. The kidney enclosed in glass wool insulation was allowed to freeze from one side to the other. Two and a half hours later when the thermocouple in the center of the kidney read −180°C., the kidney was placed into a Dewar flask holding liquid helium and the vapor pressure dropped to 80μ Hg. After a half hour at this temperature, thawing was accomplished by passing ordinary nitrogen gas through the plate, gently warming it and the kidney to 4°C. Kidneys frozen by both the aforementioned methods were retransplanted into the dog and their function compared with that of a kidney frozen to −4°C. in the ice compartment of a refrigerator.

Results. The kidney frozen and thawed by the plate or perfusion method permits the passage of a clear, glomerular filtrate for upwards to two hours. The filtrate remains grossly clear even when transplantation follows freezing to practically absolute zero if plate or perfusion thawing is utilized. However, if a kidney is rapidly thawed from −272.2°C. by immersion in 4°C. saline solution, increased glomerular damage as evidenced by a grossly bloody filtrate occurs. Microscopic sections of entire kidneys, frozen and thawed by either perfusion or the plate to −272.2°C., show only a minimal disruption of the glomerular and tubular pattern similar to changes that occur when a kidney is maintained outside the body in 4°C. saline solution for three to four hours. There was neither gross nor microscopic evidence of fragmentation.

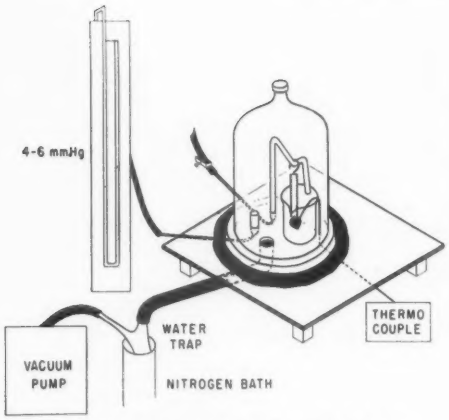

FIG. 3. Mechanical dehydration of the heart.

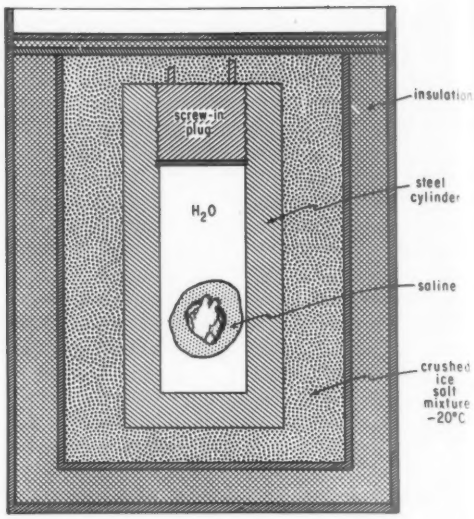

FIG. 4. Pressure method of supercooling a heart.

SUPERCOOLING OF WHOLE ORGANS

Prevention of fragmentation in itself will not permit a frozen organ to regain normal function although it lessens the injury due to freezing. Thus far attempts to saturate organs in large animals with glycerol and demonstrate viability following freezing have been unsuccessful. Following preservation of whole organs outside the body by depression of the freezing point, supercooling was next investigated. Two methods were explored.

Technic. The first approach, mechanical dehydration plus glycerol saturation, has been previously reported by Barsamian et al. [3]. A brief review follows: Hearts from puppies two to four weeks of age were removed and mechanically dehydrated in specially designed apparatus, housing a spring balance from which the heart was suspended. (Fig. 3.) Three outlets were provided; one to a pyrex jacket, surrounded by liquid nitrogen, leading to a vacuum pump; the second outlet to a mercury manometer providing for continuous measure of the vapor pressure within the chamber; the third outlet to a beaker containing either water, normal saline or 70 per cent glycerol solution. (This outlet remained clamped during the dehydration process.) As long as the vapor pressure stayed at 6 mm. Hg, the temperature of the heart during the dehydration process was 4°C. The hearts were transplanted after dehydration to the necks of recipient dogs.

Results. Seven dehydrated hearts, with upwards to 55 per cent of the water removed and replaced, showed intrinsic viability after transplantation for an average of forty hours. No heart resumed intrinsic rhythmicity following transplantation when more than 55 per cent of the water had been removed. Two hearts were dehydrated 20 and 27 per cent over three to four hours. Both of these were allowed to soak in 70 per cent glycerol solution at 4°C. for one hour. The combination of mechanical dehydration plus glycerol depressed the freezing point to −8°C. These hearts following homologous transplantation continued to beat for eight and twelve hours, respectively.

The second approach to supercooling an entire organ utilized an apparatus seen in Figure 4. Two principles were involved: (1) Water must expand to form ice. (2) The freezing point of an organ containing salt is lower than the freezing point of pure water.

In a series of experiments, hearts from dogs one month of age were removed with the dog under nembutal anesthesia. Each was placed into a sterile rubber glove containing normal saline solution which was seated in the specially constructed steel cylinder filled with water at 4°C. (Fig. 4.) After sealing, the entire cylinder was cooled by an ice-salt mixture of −19 to −20°C. and the cooling process terminated when the heart reached this temperature. Pressure developed on the heart when the water responded to its lowered temperature and attempted to expand in a closed container.

At this point, the pressure was approximately 30,000 pounds per square inch.

Periods of ischemia did not exceed six hours, well within the safe range for refrigerated hearts. The organs were then removed from the chamber and transplanted into the necks of adult dogs.

Results. The hearts studied assumed a temperature of −19 to −20°C. without freezing. Grossly and microscopically they appeared normal. However, none reacted to electrical stimulation and none resumed intrinsic rhythmicity following transplantation. The possibility of a specific injury to the conducting system is under study.

SUSPENDED ANIMATION

As part of the over-all studies in cryobiology, it was decided to study the effects of deep hypothermia to 0 to 1°C. on homograft rejection, tumor growth, and tolerance to rapid decompression. The rat was selected as the experimental animal since the excellent reports of Smith [4] and Hunter [5] indicated that the reanimation of this animal following one hour at 0 to 1°C. was possible. However, great difficulty was experienced in reanimation of rats cooled to an intracolonic temperature of 0 to 1°C. Reanimation by microwave diathermy to the chest using a commercially available apparatus and reanimation with the use of warm water to the entire animal as modified by this group are herein described.

Technic. Female albino rats of the Wistar strain, eight weeks of age, weighing 200 to 250 gm. were used. The animals were deprived of food but allowed water *ad libitum* for twelve to fifteen hours before the experiment. Each rat was placed into a sealed glass jar with a capacity of 1,800 cc. This was then inserted into a refrigerator at 4°C. and the rat allowed to rebreathe its own carbon dioxide. After 90 to 105 minutes when the animal appeared narcotized it was removed from the jar. (The optimum point to remove the rat is when the Righting reflex disappears, at which time, the average intracolonic temperature of the animals was 20 to 22°C.) It was washed with water at 1°C. to drive the air from its fur, positioned in a stainless steel tray, and covered with finely chipped ice except for the snout. Ice cold water was then poured over the animal, hastening the drop in intracolonic temperature which reaches 5 to 6°C. in twelve to fifteen minutes.

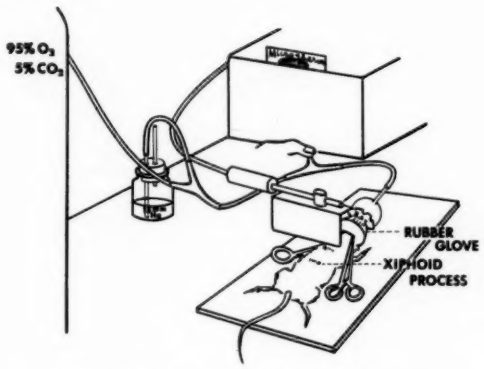

FIG. 5. Diathermy technic of reanimation.

During the process of suspended animation, the corneal reflex becomes sluggish at 15°C., disappearing at 12°C. Respirations cease at 8 to 9°C. Cardiac activity was recorded by electrocardiogram at 3 to 4°C.

The animal was considered to be in a state of suspended animation when the intracolonic temperature reached 0.5 to 1°C. It was maintained in this state for forty-five to ninety minutes. After ninety minutes, no rat could be reanimated. Rats suspended for between seventy-five to ninety minutes were frequently revived only to die within two hours irrespective of the reanimation procedure employed.

Reanimation, using the Raytheon microtherm apparatus, was perfected to the point at which 75 to 80 per cent of the animals in suspended animation for sixty to seventy-five minutes could be reanimated and survive. (Fig. 5.) Two of the initial problems encountered were the sensitivity of the terminal ileum and the limbs to the microwave diathermy. Ultimately, the limbs and abdomen were covered with aluminum foil while the beam was concentrated on the chest. Twenty per cent of the power of the machine for five to six minutes was the optimum time for successful reanimation.

In later experiments warm water at 42 to 45°C., a modification of the Hunter method [5] was used. (Fig. 6.) The reanimation rate with warm water was better than with microwave diathermy. Over 90 per cent of the animals were successfully reanimated after sixty to seventy-five minutes in suspended animation. Warm water is recommended by us for reanimation.

The critical feature of the reanimation pro-

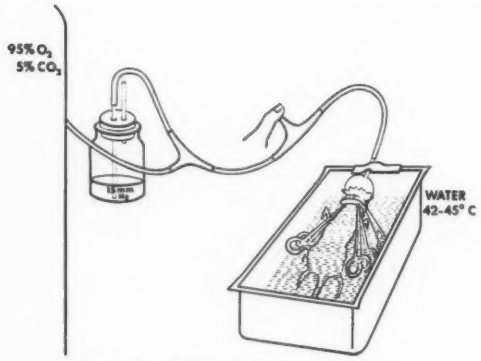

FIG. 6. Water bath technic of reanimation.

cedure was not the type of warming but the method of artificial respiration. As can be seen from Figure 5, the rubber diaphragm over the thistle funnel was made from a surgeon's glove wrapped over the funnel. It proved necessary to insert the entire head of the animal into the funnel through the opening in the rubber diaphragm in order to obtain effective artificial respiration which was maintained at a rate of twenty to twenty-five per minute. While administering artificial respiration, a finger was placed over the open end of the "T" connecter during the inspiratory phase and the finger removed from it during the expiratory phase. Pressure of the gas was controlled with manometer set at 15 mm. Hg. (Fig. 6.)

Within thirty minutes after the reanimation procedure had begun, the animals were breathing without aid. They were placed into a 30°C. atmosphere for an additional two hours, breathing 95 per cent oxygen, 5 per cent carbon dioxide, and returned to their cages without additional care.

The Effect of Deep Hypothermia on the Survival of Homologous Skin Grafts. After the technic of deep hypothermia had been perfected, split thickness grafts taken from the backs of black rats were sutured to the backs of white rats while they were in suspended animation. Fifteen rats were so evaluated. All were maintained in suspended animation for periods of forty-five to sixty minutes and the results compared with fifteen control rats not put through suspended animation. Deep hypothermia to the point of respiratory or cardiac arrest maintained for sixty minutes did not produce any prolongation of survival or alteration in the histologic rejection pattern.

The Effect of Moderate and Deep Hypothermia on Experimental Tumor Growth. A subcutaneous chloroma tumor of the Shay variety was utilized in these studies. This tumor was evaluated in our laboratory by the subcutaneous injection of 0.5 cc. of the tumor material into the mid-back area of fifty female Wistar rats four weeks of age. In forty-four animals palpable tumors developed one month after injection. Once established, the tumor usually grew very rapidly. Ten per cent of the rats exhibited metastatic lesions. Spontaneous regression occurred in four animals. After control characteristics for this tumor had been established, studies were performed on both the prophylaxis and treatment of this test system with hypothermia. Five groups of animals were evaluated.

Group I: Prophylaxis of tumor development in twenty rats. (Intermittent systemic hypothermia.)

Within five minutes after the subcutaneous injection of tumor material, hypothermia was instituted. Each rat was placed into an individual sealed 2 L. jar which was then refrigerated at 4°C. At the end of one and a half hours, the rectal temperature had reached 20 to 22°C. and the rat appeared narcotized from the rebreathing of its own carbon dioxide. Each was removed and allowed to recover spontaneously at room temperature. This hypothermia procedure was repeated once daily for thirty days, the "incubation" period for this tumor. No clinical or histologic alteration of the tumor was observed.

Group II: Prophylaxis of tumor development in twenty rats. (Cold adaptation of whole animals.)

Immediately after the subcutaneous injection of tumor material, the rats were moved into cages and left in a laboratory refrigerator at 4°C. for thirty days. Adequate food and water were provided and the temperature checked once daily. The refrigerator door was opened at least once every eight hours to prevent excessive carbon dioxide accumulation.

During the first few days of refrigeration, the rectal temperature of the rats ranged from 36 to 38°C.; subsequently, the rats were able to maintain normal body temperatures. Five rats died during the procedure.

At the end of thirty days, only three of the fifteen surviving rats exhibited palpable tumors as compared with almost 100 per cent of the

controls. These animals were then placed into cages at room temperature. One week later 80 per cent had palpable tumors. No subsequent clinical alteration was demonstrated.

Group III: Therapy of chloroma tumors in twenty rats. (Intermittent systemic hypothermia.)

Tumors of approximately 1 cc. in size were palpable in all the animals of this group. Systemic hypothermia from 20 to 22°C. by the closed vessel technic described in Group 1 was completed once daily for thirty days. This group did not differ from the controls.

Group IV: Therapy of chloroma tumors in twenty rats. (Cold adaptation.)

In this group, the animal was maintained in a 4°C. atmosphere after the tumor had reached the size of a 1 cc. The procedure which was continued for thirty days, was the same as outlined in Group II. Clinical course and histologic pattern of the tumor were similar to the control rats.

Group V: Therapy of chloroma tumors in twenty rats. (Effect of repeated deep hypothermia on tumor growth.)

Each animal was placed into suspended animation with hypothermia, the first bout being instituted at the time the tumor was 1 cc. in size. The rat was refrigerated in a 2 L. glass jar at 4°C. until it became narcotized. It was then removed from the jar and encased in crushed ice. Each was maintained without cardiac or respiratory activity for sixty to seventy-five minutes. During forty-five minutes of this time, the rectal temperature was recorded at 1°C.

After this extreme hypothermia, the rats were removed from the ice and reanimated with a combination of artificial respiration and short wave diathermy to the chest. This procedure was repeated three times on a weekly basis.

Fifteen animals withstood three episodes of suspended animation. One of these showed remission of its tumor. Over-all, the clinical course and histology of the tumor were the same as in the control group.

INFLUENCE OF DEEP HYPOTHERMIA ON THE TOLERANCE OF RATS TO INCREASED ATMOSPHERIC PRESSURE

Hypothermic rats have been shown to possess increased resistance to radiation and electric shock.

It has long been known that animals in which the vascular system takes no part in respiratory exchange are immune to decompression sickness. In 1908 Greenwood [6], exposed active third year caterpillars of the goat moth to twenty-seven atmospheres pressure for more than two hours. Air in these animals is conveyed directly to the body cells by fine branching tubes and the vascular system presumably takes no part in the interchange. After instantaneous decompression, these organisms appeared unharmed. A state in which the circulation is separate from the respiration cannot be created in higher animals; however by producing suspended animation, a situation has been achieved in which the animal has neither an active circulation nor respiration.

It was postulated that rats cooled to the point of cardiac and respiratory arrest might be more resistant to gaseous pressure than normal rats. Interest in the problem stems from the known destructive effects of pressure on viruses and some tumors. Toleration of such increased pressures would make it theoretically possible to supercool entire animals.

Prior to an evaluation of the pressure tolerance of hypothermic rats, studies were performed on live rats placed into a specially designed pressure chamber.

Technic. The compression chamber used was a steel cylinder 18 inches high and 5 inches in diameter. One end of the chamber provided an inlet for gas which was used to produce compression. The opposite end provided an inlet for the experimental animal.

The limbs of the animal were connected to an electrocardiogram machine and oxygen used for raising the pressure within the chamber. The effect of pressure was observed on the electrocardiogram of the animal. Raising the pressure from one atmosphere to 500 pounds per square inch caused no abnormality on the electrocardiogram except for a slight tachycardia.

The pressure was increased at fairly rapid rates, a half hour being required to raise the pressure from one atmosphere to 2,000 pounds per square inch. At 1,200 pounds per square inch, there was some slowing of the heart beat but at this point, the rate was the same as at the beginning of the compression. At 2,000 pounds per square inch, pressure on the breathing, unanesthetized animal, caused definite bradycardia and a slight diminution in the

voltage unit. Following 2,000 pounds per square inch, slow decompression was performed but death occurred when the pressure was recorded at 700 pounds per square inch. At autopsy, the animal showed gas bubbles in the circulatory system, peritoneal cavity and even subcutaneous tissues.

In another group of control rats, the animals were lightly anesthetized with nembutal and placed into the pressure cylinder. A mechanism for the absorption of carbon dioxide by soda lime pellets was incorporated. Twelve rats were subjected to compression for five minutes with an 80 per cent helium and 20 per cent oxygen mixture. In six the gauge pressure was recorded at seven atmospheres above ground level, eight atmospheres absolute pressure. Sixty seconds were required to raise the pressure to the required compression, twenty seconds were needed to decompress the chamber. After rapid decompression, the cylinder was opened and the rat removed for evaluation. Three of six rats which has been exposed to five minutes compression at eight atmospheres absolute pressure with helium-oxygen died after rapid decompression. Six of six rats died after rapid decompression from twenty atmospheres absolute pressure with an 80 per cent helium and 20 per cent oxygen mixture. Gas bubbles were pronounced in the circulation of all animals that died.

Fifteen rats were put into suspended animation using the previously described technic. Fifteen minutes after electrical cardiac activity had disappeared, the animals were placed into the compression chamber. Intracolonic temperature at this point was 1°C. Three gas mixtures were employed. Five rats were compressed with 80 per cent helium and 20 per cent oxygen, five rats were exposed to pure oxygen pressure, and five to pure nitrogen pressure. Five hundred pounds compression was built up in sixty seconds and decompression was accomplished in twenty seconds. The rats were then removed from the cylinder and reanimated with the warm water technic.

Results. Fourteen of fifteen hypothermic rats survived rapid decompression from 500 pounds per square inch absolute pressure. Total period of suspended animation was less than thirty minutes. It was eventually determined that 650 pounds absolute pressure was the maximum pressure consistent with survival after rapid decompression using helium-oxygen, oxygen, and nitrogen. Above 650 pounds per square inch for longer than two minutes, reanimation was possible but the animals soon died. The findings post mortem were alveolar rupture and gas bubbles within the blood stream. These were usually found in the right auricle or right ventricle, and pulmonary artery, thus indicating an origin of gas bubbles in the venous system.

Suspended animation protects the rat during rapid decompression from pressures as high as 650 pounds per square inch.

COMMENTS

If the deterioration of frozen tissue obeys the Arrhenius equation, it is not likely that temperatures below liquid nitrogen (−196°C.) will be necessary for long term storage; nevertheless it is of interest that human tissues will withstand temperatures approaching absolute zero. As previously mentioned a solidly frozen dog kidney will not regain normal function following transplantation. The irreversible damage occurred between −2 to −4°C. A kidney frozen by usual technics to −4°C. and retransplanted, will exhibit marked glomerular dysfunction, producing a bloody glomerular filtrate. The technics for freezing and thawing, herein described, do not permit a solidly frozen kidney to function normally after transplantation, but they do minimize glomerular damage as evidenced not only by microscopic findings, but by the production of a clear glomerular filtrate by a kidney frozen to −272.2°C., thawed, and retransplanted.

When an entire organ is frozen by a method which permits a shell of ice to form on the surface, the continuous expansion of water during the freezing process causes fragmentation. Both the perfusion and plate technics, by eliminating the encircling shell of ice permit water to expand without fracturing the organ. Plate or perfusion thawing is more rapid than allowing the kidney to thaw at room temperature. The fact that plate or perfusion thawing of a kidney causes less glomerular damage than occurs when an entire organ is frozen to −272.2°C. and thawed in a 4°C. saline solution remains unexplained.

A combination of mechanical dehydration and glycerol saturation allows cooling of the dog heart to −8°C. without freezing. These were rehydrated, warmed and homologously transplanted resuming a beat. It is inferred

that it is not cooling *per se* but the insult of freezing which results in irreversible injury to the heart.

It is possible to depress the freezing point of entire hearts to −20°C. This was accomplished by producing pressure secondary to cooling. When red blood cells are subjected to this technic, they fracture under pressures of 30,000 pounds per square inch. However, red cells are not injured by pressures of 50,000 pounds per square inch at room temperatures. Red blood cells can be saturated with glycerol, frozen to −79°C. and will maintain viability. Embryonic hearts, after 1,850 atmospheres pressure, will continue to grow in tissue culture [8].

The lethal effect on these supercooled hearts may come from the simultaneous combination of temperature reduction and pressure. In general, pressure tends to shift the equilibrium of any reversible reaction in the direction of a lesser volume, and temperature tends to shift it in the other direction. An increase of temperature counteracts the effect of pressure on the amoeba. At 10°C. it takes 3,000 pounds per square inch to stop motion of the amoeba and at 25°C. it takes 6,000 pounds per square inch to stop the motion. These are reversible reactions [9]. Experiments are now under way to determine whether hearts can be placed under pressure and then supercooled. It is hoped that the prior application of pressure may permit entire organs to maintain viability following cooling. The relationship between pressure and freezing point depression is shown in Figure 7.

Systemic hypothermia was first used clinically as a method of influencing the growth of malignant tumors by Smith and Fay in 1938 and 1939 [10]. They reported that general refrigeration might offer a valuable therapeutic adjunct in the treatment of undifferentiated cell growth, particularly of carcinoma. Experimental research on the problem of the effect of systemic cooling on the prophylaxis and treatment of malignant tumor growth is unfortunately scanty and conflicting.

Two considerations prompted this study in the hypothermic animal. The first was the recent interest in Russian medical literature on the favorable influence of systemic hypothermia on the growth of experimental tumors and the second was the technic for reanimation of rats with body temperatures of 0 to 1°C.,

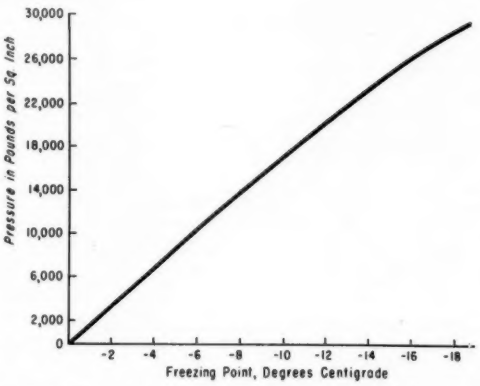

FIG. 7. The relationship between pressure and freezing point depression.

which has been refined in this laboratory to a point where the animal will survive repeated one hour bouts of suspended animation.

The effect of temperature on growth has been shown by many investigators. Organs or body areas with higher temperatures have a higher incidence of malignant growth [11]. Lowered body temperature as employed in these experiments was of no value in the therapy of the subcutaneous chloroma tumor in rats. Previously, Mandrik [12] and Niazi and Lewis [13] had reported the favorable influence of systemic hypothermia on experimental tumor growth. These investigators used the Brown-Pearce tumors, the Flexer-Jobling carcinoma, the Jensen sarcoma, and the Walker carcinosarcoma 256. The chloroma tumor used by us has a very low incidence of spontaneous regression. Repeated hypothermia to body temperatures of 0 to 1°C. was followed by neither histologic tumor alteration nor gross regression of the subcutaneous chloroma tumor.

Pressure has become a useful tool in physiology. The sensitivity of many viruses and certain tumors to pressure has been demonstrated. For the most part, hydrostatic pressure has been utilized but the possibility of applying various gases to the compression of laboratory animals as well as to viruses and isolated organs merits more study. In these preliminary experiments, the hypothermic rat without active circulation or respiration was shown to be markedly more resistant to brief periods of compression by gases and rapid decompression than the normal rat. Less gas per given time and pressure gains entrance to the circulation

through the lungs and skin in animals cooled into suspended animation than enters the circulation of breathing normothermic rats.

Many hurdles must be overcome before the rat in suspended animation secondary to hypothermia can be made to tolerate pressures above 650 pounds per square inch. One limiting factor appears to be a condition similar to traumatic air embolism. If a person in escaping from a sunken submarine, instead of forcibly exhaling, holds his breath and ascends to the surface, the intrapulmonic pressure becomes higher than the hydrostatic pressure and this difference over-distends the lungs, ruptures the alveolar sacs and blood vessels and forces gas into the blood stream. This appears to be one of the major reasons for death when a rat in suspended animation is subjected to pressures greater than forty-five atmospheres for longer than two minutes or greater than thirty-five atmospheres for longer than five minutes. Obviously, residual air is present in the thoracic cavity in the animal possessing neither active respiration nor circulation. Another limiting factor is that gases will pass slowly through the skin and mucous membranes even in the hypothermic animal and it appears that an animal without active circulation is not so readily decompressed as one with active circulation. The human body can be compressed to almost eighteen atmospheres, equivalent to a diving depth of 150 feet, without demonstrable physiologic effect, provided air has free access to all body surfaces. Cattell [*14*] has shown that pressure up to several hundreds of atmospheres is well tolerated by protoplasm.

The ultimate aims of this work are to make possible long term preservation of entire organs outside the body at reduced temperatures applying the lessions learned from the organ work to the entire animal.

The state of suspended animation in homothermic animals including man offers intriguing possibilities in an age of exploration of the atmosphere.

SUMMARY AND CONCLUSIONS

1. Human conjunctival cells will maintain viability when saturated with 6 per cent glycerol solution, frozen to −272.2°c. and thawed in a 26°c. water bath. Sixty per cent of human spermatozoa saturated with glycerol, subjected to temperatures approaching absolute zero, are motile after thawing. Ten per cent of human spermatozoa without glycerol remain motile following thawing after a half hour at temperatures within one degree of absolute zero.

2. Technics to minimize the physical effects of freezing to very low temperatures on the canine kidney are presented. In one of these, the kidney was frozen by way of its vasculature. In the other technic, the kidney was frozen on a specially designed plate. Function was not preserved although the kidney appeared grossly normal and microscopic damage was minimal.

3. Canine hearts can be dehydrated up to 55 per cent of their water, rehydrated, and will resume intrinsic rhymicity following transplantation. A combination of mechanical dehydration and glycerol saturation will permit canine hearts to be supercooled to −8°c. without freezing. These hearts can be resuscitated by transplantation. Hearts supercooled to −20°c. with pressure did not resume function following transplantation.

4. Deep hypothermia has no effect on the prolongation or histologic rejection pattern of homologous skin grafts in the rat.

5. Neither intermittent moderate hypothermia nor cold adaptation lessened the take of a subcutaneous chloroma tumor in rats; however, cold adaptation delayed the clinical palpability of this tumor. Cold adaptation, intermittent moderate hypothermia, and deep hypothermia to the point of respiratory and cardiac arrest were performed on Wistar rats harboring chloroma tumors. No regressions were observed.

6. Rats cooled to a state of suspended animation at 1°c. without circulation or respiration will tolerate rapid decompression after 650 pounds compression per square inch.

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DISCUSSION

WILLIAM P. LONGMIRE, JR. (Los Angeles, Calif.): Drs. Dunphy and Jacob are to be congratulated upon these extensive, fundamental studies.

Woodruff states that the factors which determine the fate of frozen cells have not been fully elucidated, but the following variables have been shown to be important: (1) cell permeability; (2) rate of cooling; (3) treatment with glycerol and other substances; (4) conditions of storage; and (5) the rate of thawing.

In regard to cell permeability, the amoeba which has a relatively impermeable cell membrane undergoes little change in the composition of its protoplasm as it is cooled, whereas most mammalian cells which have a cell membrane which is highly permeable to water become dehydrated as the temperature is lowered and may actually be killed by dehydration if the cooling process is slow.

Rapid freezing produces intracellular ice crystals which are so small they are relatively innocuous.

The protective action of glycerol is not fully understood. It seems, however, that it acts as a diluent and lowers the concentration of salt which is in equilibrium with ice at any given temperature and secondly, it reduces the speed of crystallization and the size of the crystals which are formed.

There is evidence to indicate that supercooling to −190°C. or to −272.2°C., as used in the present experiments, may permit cells to retain their viability for longer periods of time than when stored at −79°C. or higher temperatures. Smith and Parks have demonstrated viability of ovarian tissue frozen at −190°C. for as long as 367 days. They state that the damage caused by freezing and thawing is not increased by prolonging the period of storage at −190°C. from an hour to a year. They even suggest that tissue under these conditions is potentially immortal.

It is generally agreed that rapid thawing as utilized in the present experiments is less damaging than slow thawing.

From the relatively simple studies of cooling individual cells the authors have moved into the highly complex studies of cooling organs and whole animals. Their technics of cooling kidneys to −272.2°C. on the specially designed plate or by perfusion with liquid nitrogen are particularly fascinating. The lack of histologic destruction and the production of a clear glomerular filtrate following rewarming are encouraging results, but of course indicate that these technics are not yet perfected to the point where they would provide a useful method of storing organs for subsequent transplantation.

Andjus of Belgrade apparently first demonstrated in 1951 that adult rats could be revived after cooling to 1°C. These observations have been confirmed and extended by Smith, Lovelock, Parks and others including the present authors. The lack of effect of hypothermia under the conditions of the experiments on transplanted tumor tissue herein reported is disappointing but apparently confirms the fact that tumor tissue, when cooled in the intact body of the host, responds somewhat as it does when isolated, for freezing is now being used as a convenient method of storing viable tumor tissue for laboratory studies.

It is difficult to express adequate admiration for the great volume of highly significant experimental data presented in this paper, for the ingenuous methods by which these problems have been attacked, and the beautiful manner in which the material was presented

LUCIUS D. HILL (Seattle, Wash.): The fascinating work that Dr. Dunphy is doing has interested us for some time. Whereas Dr. Dunphy has been utilizing cold to preserve tissue, Drs. John Tytus and Lincoln Reese, working in our laboratory, have been utilizing cold for another purpose, namely, the destruction of tissue.

Dr. Tytus and Dr. Reese have devised a probe with which they hope to eventually selectively destroy areas of tissue almost anywhere in the body that are inaccessible to surgery by present technics. This is a cold probe using freon, which develops a tip temperature of minus 41°C.

After this probe has been in place for about fifteen minutes, an area of brain tissue measuring 1½ to 2 cm. in diameter is destroyed.

Sections taken two weeks after freezing by this method show a rather sharp demarcation between viable tissue below and non-viable tissue above.

This has led Dr. Tytus and Dr. Reese to believe that this is a relatively selective method of destroying tissue.

These probes have been inserted through the hard palate into the pituitary fossa in an effort to perform a bloodless hypophysectomy by this method, but using a probe with a tip temperature of −41°c. does not entirely destroy the pituitary. A small area of viable pituitary remained in all dogs studied. Consequently Dr. Tytus and Dr. Reese are now working with a different probe with a tip temperature that reaches −141°c.

With this more refined probe they hope not only to apply this to such areas as the pituitary, but perhaps in tumor surgery to freeze a tumor, fix it in place, and then remove it without spillage of tumor cells and without blood loss.

This is simply an extension of the exciting work that Dr. Dunphy is doing, and it is gratifying to know that a provocative and stimulating mind such as Dr. Dunphy's is working in this area. We believe that this will open new vistas in the field of surgery.

STANLEY W. JACOB (closing): For years man's principal interest in freezing was his defense against it. Work such as Dr. Hill mentioned shows that this medium does have potential long-range significance to the surgeon.

To summarize some of this material, there are in general three ways to preserve tissue with the use of cold, and these three ways carry through whether one is preserving an isolated cell, a whole organ or an entire animal.

The first of these, of course, is to freeze the tissue so rapidly that no crystals form outside the cell. This is a highly technical method, and only applicable to very small bits of tissue such as a few red cells sprayed on to liquid nitrogen.

The second general method is to freeze the tissue slowly with the use of a protective agency such as glycerol. As Dr. Longmire mentioned, no one really knows the function of glycerol. What it probably does is simply to tie up a certain amount of water within the cell so that less water is available for crystallization. Even with glycerol tissues will demonstrate ice crystal formation but of a lesser degree, and the crystals exhibit a different geometric form from nonglycerolized frozen tissues.

The third general approach, and the one in which we are most interested, is undercooling or supercooling, or depressing the freezing point. There is a difference between freezing and supercooling. A frozen organ is a hard organ which is filled with ice. Once frozen, it will never resume normal function. An undercooled or supercooled organ is a soft organ and one in which the freezing point has been depressed. It merely assumes a temperature well below the point of ice formation, and we hope that with this technic of undercooling or supercooling we can maintain for prolonged periods whole organs outside of the body.

Eventually, of course, the cryobiologist will aim at a state in which tissues will not merely be preserved at very, very low temperatures, but preserved in a viable state at room temperature. Theoretically this would be possible if one used a substance such as methanol to protect against freezing, froze the tissue solid to −40 to −80°c., then removed both the methanol and water and kept this tissue at room temperature. Some interesting experiments along these lines have already been performed by the group in Mill Hill in London.

It is of interest to mention that the Russians believe that the only logical approach to preservation of the whole organ or the whole animal, for that matter, is the technic of supercooling or undercooling, and they are performing some experiments with the supercooling or depression of the freezing point on whole animals, not with the two media which we are utilizing but by other technics.

Suspended animation in itself will protect against radiation damage, lethal electric shock, and, as we have shown, against rapid decompression. I think that eventually some of this work on the whole organ will be applicable to the entire animal. The state of suspended animation in homothermic animals, including man, offers intriguing possibilities in regard to the upper atmosphere.

Surgical Management of Dyskinesia

EDWIN M. TODD, M.D., C. HUNTER SHELDEN, M.D., ROBERT H. PUDENZ, M.D. AND BENJAMIN L. CRUE, JR., M.D., *Pasadena, California*

DISORDERS of motion have attracted surgical interest since very early times. This is clearly evident in the trephined skulls found among the vestiges of ancient peoples, some predating the dawn of recorded history, from widespread areas about the world. Entry into the cranial vault of the maimed or the mad was accomplished with wondrous skill in some instances by our neurosurgical predecessors, presumably to release the guilty evil spirits. Whereas motivation has been somewhat more realistic in our time, until very recently, surgical measures proposed to alleviate dyskinesias were successful only insofar as they substituted paresis for the less desirable state. That such an appalling exchange was acceptable, merely indicates the wretched unhappiness and disability of these patients and emphasizes the inadequacies of other forms of therapy. The outlook has been vastly altered during the past decade as certain target areas within the complex network of deep central brain structures have been identified by a succession of "inadvertent" incidents as sites wherein the placement of destructive lesions will effect variable relief of tremor, rigidity, chorea, ballismus, athetosis, and other dystonic states.

While the pathophysiologic mechanisms involved in the cause as well as the cure remain obscure, it is quite clear clinically that it is possible to abolish any or all of these disturbances without interfering with strength or function, and without incurring significant mental or physical deficits. This is not to imply that all cases can be cured, but it becomes apparent, as experience enlarges, that gratifying improvement may be anticipated in at least 75 per cent of operable patients. Age, duration and severity are not important factors in assessing results from the standpoint of symptom relief; however, morbidity and mortality follow linear ascents with increasing age brackets. Existing mental impairment or psychosis is likely to be accentuated. Poor surgical risk patients, by general medical criteria, should be screened out.

The stereotactic treatment of rigidity is well established. Abolition of tremor has been less publicized although it appears equally amenable to surgical intervention. Undoubtedly, this lag is attributable to the natural time sequence in the evolution of basal ganglia surgery as attention was at first focused on the mesial globus pallidus. It was noted that rigidity consistently responded more favorably than tremor to properly placed lesions. As the volume of reports increased, relating to the rather dramatic cessation of tremor which often attended the inadvertent introduction of instruments too far posteriorly, subsequent investigation identified the site as the ventrolateral nucleus of the thalamus and new vistas were opened for the stereotactic surgeon. It is now the usual practice to attack the thalamic nucleus initially if tremor is the dominant symptom and, indeed, it is generally conceded that mixed disorders of motion are more favorably altered by lesions in this area.

These improbable therapeutic rewards evolving from a process of surgical roulette would appear, at first glance, to accentuate the irony of earlier frustrations resulting from experimentation based on more scientific principles. Actually, the empirical observations deriving from the chain of accidental discoveries which have characterized the development of stereotactic surgery have served as immensely valuable touchstones in the reappraisal of our concepts of extrapyramidal function. Knowledge of the true anatomic and physiologic relationships is enriched daily as data accumulate from experimental, operative and autopsy experi-

FIG. 1. An instrument designed to provide a simple, efficient holder and guide for the introduction of electrode or cannula into the deep central target areas.

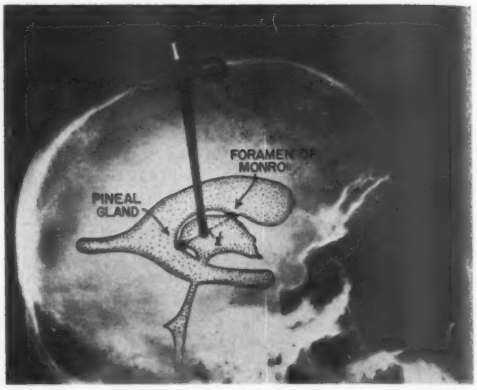

FIG. 2. Illustrates an ideal situation for placement of the cannula tip on the lateral projection in accordance with Cooper's postulates.

ence. Even so, the attainment of gratifying clinical results at this point is still more an art than a science.

Our experience now comprises 133 cases and covers a span of five years. We have discarded the leukotome as too hazardous, and coagulation technic as less rewarding. We prefer chemical destruction of the target areas by fractional production of a gradually enlarging lesion, utilizing Etopalin via a Cooper double lumen balloon cannula, supported by a Todd-Heyer cannula guide. (Figs. 1 and 2.)

We have depicted in a short film the anatomy and principles of surgical management of a patient who was an illustrative case. (This film was presented as part of this report.)

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DISCUSSION

DAVID REEVES (Santa Barbara, Calif.): In 1817 Parkinson said he would think himself fully rewarded by having excited the attention of those who may point out the most appropriate means of relieving a tedious and distressing malady. The quest for this goal has continued, but unfortunately most of the surgical procedures in the past, which were often ushered in with enthusiasm, have now become matters largely of historical interest.

Narabayashi and Cooper, with their methods of injecting procaine into the globus pallidus for the treatment of hyperkinetic disorders, have been responsible for a renewed interest in the surgical approach to this intriguing problem, and a new school of neurosurgeons devoting their time mainly to this field and often facetiously called "needle neurosurgeons" has arisen.

Whether the neurosurgical answer will be that of injection, leucotome, electrolysis, ultrasound, the proton beam of the cyclatron or some other as yet unrevealed method yet remains to be seen.

One might say that this interesting work of Drs. Shelden and Todd represents an additional step in the continuing search for The Golden Fleece of permanent abolition of the disabling symptoms of Parkinson's disease and other hyperkinetic disorders.

W. EUGENE STERN (Los Angeles, Calif.): Dr. Sheldon's presentation was most impressive, very enjoyable, and up to his standard of excellence in film production; I compliment him on an obviously dramatic improvement in this patient as shown in the motion picture.

I would like to be able to say that the experience at the University of California at Los Angeles in the hands of my associates in the Division of

Neurological Surgery, specifically Drs. Robert Rand and Paul Crandall, had been as uniformly successful as this case presented by Dr. Sheldon.

The fact that the experience has not been as sanguine has led, therefore, to an effort to improve our knowledge of the abnormal physiologic mechanisms that are at work in this debilitating disease and to develop technics to improve surgical therapy for it.

It would be proper, I believe, to record some of the complications that have resulted from utilization of the technic which has been so expertly illustrated here today and which was perfected by Irving Cooper, based upon the studies of Spiegel, Wycis and other investigators prior to Cooper's contribution.

My colleagues devote themselves to this technic, not exclusively as "needle neurosurgeons," but because it is required for gaining perfection in it; and for this reason also, we limit the treatment of this particular case material to a small team.

The first complication which is observed is that paresis will develop in patients at times, without the introduction of the alcohol, after the balloon had been inflated. At times a motor disturbance is not overt, yet with the release of tremor the patient still will not utilize the extremity from which the tremor has been ablated although there may be little objective evidence of weakness.

We have observed a series of patients who, following this procedure, have had abnormal movements superimposed upon or replacing the Parkinson tremor; these are choreiform-athetoid or ballistic movements which have replaced, fortunately temporarily, the abnormal tremor which had been present as the original manifestation. These, as I say, are temporary but may last as long as two weeks following the procedure. They are disturbing to the patient and to the physician.

Intracerebral hemorrhage can occur with the inflation of the balloon without the alcohol. It can be catastrophic, fortunately, in a very small number of patients. We have had two deaths from this complication in a series of patients, approaching 150 in number, treated by the described technic.

Intracerebral abscess is another complication which we would like to feel could not occur in an elective procedure, yet in the literature as well as in our experience this has also been a complication.

The mental obtunding which occasionally results, particularly if bilateral lesions are placed, is also disturbing and may preclude the return of the patient to useful life.

Because of these complications in the utilization of this technic, we feel that there is room for further study in the development of other technics and tools which will permit not only the investigation of the abnormal pathologic mechanisms that are at work in this disease, but to measure them and to learn how to balance the abnormal circuits correctly. Such studies are leading to the development of different technics in the hands of the numerous investigators studying this disease.

I should like to thank Dr. Shelden for a very nice presentation. I do not like to sound a grim note but merely wish to balance the picture.

JOHN C. WILSON, JR. (Los Angeles, Calif.): The orthopedic surgeon has more than a passing interest in what Dr. Shelden has to say. I have been tried many times in treating patients both before and after their stereotactic procedures.

The treatment of fractures in patients with Parkinsonism has always been most difficult. I think if you recall the man that you saw a few moments ago (in the film) who was struggling, in spite of his tremors, to read the *Wall Street Journal*, you can imagine what it would be like to treat such a patient for a fracture of both bones of the forearm.

The practical aspects of treatment are formidable and it has been necessary to rely upon open reduction with firm internal fixation. Even this frequently leads to nonunion.

These patients tolerate major surgical procedures poorly. They tolerate a long convalescence even less well. Muscular weakness following the stereotactic procedure is a very real problem; the only word of caution that I could interject is that when they first get out of bed they must be accompanied, and their weight bearing must be protected. A fracture of the femoral neck either before or after their surgical procedure is indeed a major disaster. The treatment of hip fractures at best is difficult, but when it occurs in patients with this disease it is sometimes almost an impossible problem, and the orthopedic surgeon has had to fall back upon primary prosthetic replacement in an effort to rehabilitate these patients.

I feel honored to have had a chance to say a few words and congratulate Dr. Shelden on his excellent movie.

C. HUNTER SHELDEN (closing): I appreciate the discussants mentioning many of the problems which exist. I am sure that we are all well aware that even though this problem is old, the treatment and the methods of treatment are relatively new. There are so many bizarre aspects to movement disorders, spasticity and tremor and combination that no one at the present time understands fully which patients are, other than those with the most characteristic syndromes, amenable to such therapy. Although this method produces excellent therapeutic results in a large percentage of patients, it is obvious that a good result is not necessarily synonymous with a better understanding of the etiologic factors and I am certain, as are those interested in this problem, that the final evaluation and the proper selection of patients as well as the selection of present therapeutic methods and development of new ones depends largely on our future better understanding of the basic pathophysiologic factors which are involved.

Ruptured Aneurysms of the Aortic Sinuses of Valsalva

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THE AORTIC sinuses of Valsalva are largely intracardiac in position. The medial wall of each sinus is an aortic cusp; the lateral wall the ascending aorta. A congenital weakness of this portion of the aorta consisting of a lack of continuity between the media of the aorta and the annulus fibrosis of the aortic valve ring predisposes to aneurysmal dilatation. Rupture of the aneurysm leads to an aorticocardiac fistula which imposes a severe burden on the heart and frequently leads to an early death.

The first detailed description of this interesting entity was made by Thurnam [1] in 1840. In the classic paper by Morgan Jones and Langley [2] in 1949, twenty-five cases of congenital aortic sinus aneurysms of which twenty-one led to aorticocardiac fistulas were reviewed. In addition, their review encompassed twenty-two acquired aneurysms confined to the aortic sinuses, only six of which were complicated by intracardiac rupture. In addition to the essential etiologic difference, they stressed the clinical differences between these two types of aneurysms. The former are small and almost always confined to the right coronary sinus and adjacent two thirds of the noncoronary sinus and commonly rupture to form aorticocardiac fistulas, while the latter may arise from any of the aortic sinuses, are large in size, tend to extend upward and often rupture outside the heart. Of these twenty-two acquired aneurysms, seventeen were associated with syphilis, four with bacterial endocarditis and one was listed as dissecting and one as atheromatous. Because of the decreased incidence of syphilis and better medical therapy, the number of such acquired aneurysms has decreased in recent years. In 1955, Oram and East [3] reviewed twenty-three cases of aortic sinus aneurysms and found that three were caused by syphilis, four by bacterial infection, and sixteen were clearly congenital.

Sawyers, Adams and Scott [4] reviewed forty-seven cases of congenital aneurysms of the aortic sinuses found in the literature to 1956, and presented an experimental plan for closure of the fistula using hypothermia and inflow stasis. Morrow et al. [5] reported another method for correction based on the passage of a plastic prosthesis from the aorta through the aorticocardiac fistula during a brief period of inflow occlusion combined with hypothermia. Since then there has been an increasing number of successful operations, using hypothermia as reported by Wigle, McKelvey and Bigelow [6], and by open heart surgery using extracorporeal circulation as reported by Lillehei et al., McGoon, Edwards and Kirklin, Kay and co-workers, Spencer, Blake and Bahnson and others [7–10].

Three cases recently have been successfully repaired by one of us (F. Gerbode) and it seems worthwhile to add these cases to the literature and discuss certain points of this fascinating entity.

CASE REPORTS

CASE 1. H. A., a forty-seven year old white married woman, was admitted to the hospital with a history of congenital heart disease, initially cyanotic. Her cyanosis improved to the point to which there was only a slight bluish tinge of her fingernails on exertion and she remained fairly well until recent years when she began having

TABLE 1
CARDIAC CATHETERIZATION DATA (CASE 1)

Catheter Position	Oxygen Content, Van Slyke (volumes %)	Blood Pressure (mm. Hg)
Superior vena cava	12.0	...
Right atrium		
High	12.8	...
Low	12.3	2 (mean)
Right ventricle		
Low	12.8	...
Low	12.7	124/5
Infund ibulum, high	13.3	18/5
Pulmonary artery		
Main	13.0	17/5 (12 mean)
Right	13.0	19/6
Left	13.3	...
Brachial artery	16.5 (92% saturation)	124/61
Pulmonary wedge	...	6 (mean)
Capacity	17.9	...

Packed cell volume = 41
Pulmonary/systemic flow ratio = 1.2:1

FIG. 1. An artist's conception of the fistula from the right coronary sinus to the infundibular chamber in Case 1.

severe fatigue, edema in the ankles, dyspnea, orthopnea, and pain in her chest and left arm on exertion. On examination, her blood pressure was 140/94 mm. Hg, and the heart rhythm was regular with no enlargement detectable. In the left third intercostal space, there was a thrill and a loud systolic ejection murmur which transmitted poorly over the precordium. This was followed by a soft diastolic murmur continuing directly after the systolic murmur. The pulmonic second sound was not loud. There was no venous distention, no liver enlargement and only slight pedal edema.

The electrocardiogram showed normal sinus rhythm, right axis deviation and abnormal T waves. A phonocardiogram showed a harsh ejection systolic murmur beginning 0.16 seconds after the first heart sound and extending through the aortic component of the second sound. The second sound was not widely split. A diastolic murmur was inconstantly recorded at the pulmonic area, disappearing by mid-diastole. Cardiac roentgenograms showed a suggestion of right ventricular enlargement, a prominence of the pulmonary artery and a normal or slightly diminished pulmonary vascular tree. A cineangiocardiogram showed a marked infundibular stenosis with a distinct infundibular chamber and an extremely slight premature aortic opacification thought to represent a right to left shunt through a ventricular septal defect. Cardiac catheterization demonstrated a moderately severe infundibular stenosis and a small left to right shunt at the level of the infundibulum. The pressure responses on Valsalva maneuver ruled out a large interventricular septal defect opening into the high pressure right ventricle. The pulmonic to systemic flow ratio was 1.2:1.0; there was no evidence of a right to left shunt. See Table 1 for data concerning catheterization. It was believed that the possible causes for the infundibular shunt were as follows: (1) a small ventricular septal defect with pulmonic valvular insufficiency, to explain the diastolic murmur; (2) sinus of Valsalva to right ventricle fistula; and (3) aberrant coronary vessel.

In October 1958, open heart surgery using extracorporeal support was performed. On exposure of the heart through a median sternotomy incision, there was a continuous murmur heard by auscultation over the outermost portion of the outflow tract of the right ventricle. By palpating through the tricuspid valve, a calcified and fibrotic protrusion could be felt in the floor of the right ventricle in the center of the infundibular chamber. A jet of blood could be felt coming through this protrusion. On opening the right ventricle, the jet was seen coming through an opening 4 mm. in diameter. (Fig. 1.) This had a hard fibrous ring

around it with a calcific area extending down to the tricuspid valve insertion. The aorta was cross clamped and the heart stopped by potassium arrest. Several mattress sutures closed the defect. An Ivalon® patch was sutured over the repair. A rather large area of infundibular stenosis was resected. The pulmonary valve was normal. The ventriculotomy was closed and the heart started in a normal sinus rhythm. After several minutes of normal systemic pressure, the pressures were measured in the right ventricle as 30 mm. Hg and in the pulmonary artery as 25 to 30 mm. Hg. The following morning a hemothorax was evacuated after which her postoperative course was free of complications.

Comment. The infundibular stenosis had largely protected this patient, for an unknown period of time, from the usual mechanism of progressive right ventricular failure. This fistula may have been congenital since there was no evidence of an aneurysmal sac found at surgery. Morgan Jones' and Langley's series included one case associated with infundibular pulmonic stenosis and Case II, reported by Kieffer and Winchell [*11*], likewise had an associated infundibular pulmonic stenosis with a fistula but no sac.

TABLE II
CARDIAC CATHETERIZATION DATA (CASE II)

Catheter Position	Oxygen Content, Van Slyke (volumes %)	Blood Pressure (mm. Hg)
Inferior vena cava	12.7	...
Superior vena cava	12.6	8
Atrium		
Right	11.8	7
Right	12.0	...
Ventricle		
Right	12.35	...
Right	14.4	59/8
Right, high	14.2	...
Pulmonary artery		
Main	14.5	54/26 (38 mean)
Main	14.3	...
Right	16.2	...
Brachial artery	16.6 (96% saturation on hyperventilation)	156/63
Capacity	17.3	...

Pulmonary/systemic flow = 2.2:1

CASE II. M. A., a thirty-one year old housewife and mother of three, was told at fourteen years of age that she had heart trouble and should, therefore, not participate in strenuous activities. She was asymptomatic until 1948 when she noted an abrupt onset of palpitation and exertional dyspnea for forty-eight hours. On examination, shortly thereafter, her blood pressure was 144/80 mm. Hg and her pulse was 110 per minute; there was no cardiac enlargement. A thrill was found in the third left intercostal space at the sternal border, and at this site there was a loud continuous murmur transmitted over the entire precordium, the right side of the chest, and the back. The liver was not enlarged and there was no pedal edema. The electrocardiogram was normal. Fluoroscopy and x-ray films of the chest showed cardiac enlargement. The left ventricle was enlarged downward to the left and posteriorly, the segment of the pulmonary artery and the pulmonary conus were quite full and there appeared to be some enlargement of the right ventricle. The hilar shadows were prominent and there was a slight hilar dance.

A diagnosis of patent ductus arteriosus was made and the patient was operated on in January 1949. A small fibrotic ligamentum arteriosum was identified. The pericardium was incised over the anterior surface of the heart. The pulmonary artery measured 3.2 cm. in diameter and the aorta 2.4 cm. in diameter. A marked thrill was present in the root of the pulmonary artery; this thrill could be obliterated by pressing on the pulmonary artery distal to the thrill as well as proximal to it. There was obvious right ventricular hypertrophy. It was the opinion of the operator that this represented some type of aortic pulmonary artery communication in the region of the root of the great vessels.

From 1949 to 1959, the patient engaged in normal activities, married and delivered three children without incident. In December 1959, because of increasing fatigue and dyspnea of one year's duration following a "virus" infection, she was carefully examined and the results were evaluated. Her continuous murmur was unchanged. A phonocardiogram recorded in the fourth left interspace parasternally revealed a systolic ejection murmur and a loud decrescendo diastolic murmur. A calcified aortic valve was seen during fluoroscopy. Cardiac catheterization (Table II) was interpreted as demonstrating a ventricular septal defect with a left to right shunt and only a moderate elevation of pressure in the pulmonary artery. A cineangiocardiogram was interpreted as demonstrating aortic insufficiency with a ventricular septal defect and ruling out an aortic septal defect as well as a sinus of Valsalva aneurysm rupturing into the right ventricle.

In May 1960, she had chills, fever and headaches with marked tachycardia. The temperature spiked

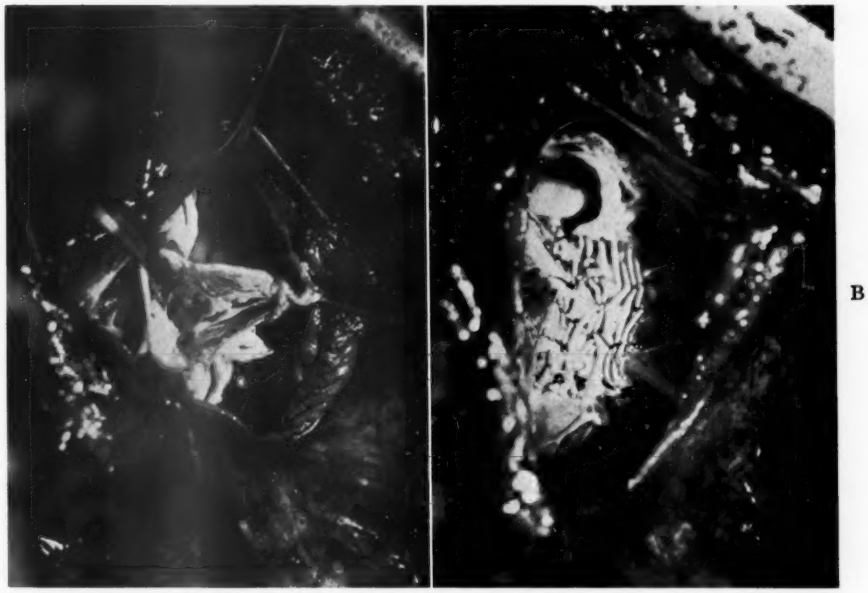

FIG. 2. A, photograph of the "ballooned out" aneurysm sac of Case II. B, shows the completed repair of the fistula and ventricular septal defect.

to 104°F. and her spleen was enlarged. No embolic phenomena were recognized but six positive blood cultures were obtained during the first seventy-two hours after admission. The organism was a Streptococcus which could not be more definitely identified. She was treated successfully with 12,000,000 units of penicillin and 1 gm. of streptomycin daily. Examination shortly afterwards showed no evidence of cardiac decompensation and it was believed that no adverse change had taken place in her cardiac status. One month later she had dyspnea with moderate exertion.

On admission in July 1960, the character of the murmur was unchanged. The blood pressure, however, was recorded as 114/0 mm. Hg. Cardiac x-ray films revealed a marked enlargement of the right atrium and right ventricle. The pulmonary artery was described as being enormous and there was marked prominence of the pulmonary vascular tree. There was no distinct evidence of enlargement of the left atrium or left ventricle but the patient was not subjected to fluoroscopy. The electrocardiogram showed normal sinus rhythm, left axis deviation to plus 60 degrees, left atrial enlargement and probably left ventricular hypertrophy. In July 1960, the patient was operated on utilizing extracorporeal circulation. On exposure of the anterior surface of the heart, there was a sharp thrill felt by palpating the anterior surface of the right ventricle. Palpation through an atriotomy revealed a calcified area at the margin of the pulmonary valve; in the center there was a strong jet of blood. Occlusion of the opening raised the diastolic pressure from 40 mm. Hg to 80 mm. Hg, indicating that there was a direct connection between the aorta and the right ventricle. The patient was placed on total heart lung bypass and cooled. The heart fibrillated at about 25°C. The right ventricle was opened and the calcification just below the margin of insertion of the pulmonary valve was seen. Around this area, there was a large saccular aneurysm. (Fig. 2.) This had ruptured widely and had granulation tissue around the edges, probably resulting from healed vegetations from the previous bout of endocarditis. Beneath the aneurysm, which arose just above the center of the right aortic cusp, there was a crescent-shaped interventricular septal defect measuring 12 mm. in diameter. By opening and closing the aorta, it was determined that the aortic valve was slightly incompetent, but most of the aortic runoff was through the ruptured aneurysm. The margins of the aneurysmal sac were trimmed, and the base was used to close the fistula and to form an imbricating layer over the sutured interventricular septal defect. Both the site of the aneurysm and the closure of the interventricular septal defect were then covered by a crimped Dacron® patch. The aortic valve was still slightly incompetent so the aorta was opened exposing the aortic valves. The right coronary cusp was found to be rather stiff and calcified and was displaced downward and away

from the two normal cusps. In order to correct the insufficiency the corners of the commissures were tacked together with two interrupted sutures. The heart was defibrillated after rewarming and a satisfactory blood pressure was maintained. On listening over the base of the aorta there was an occasional slight aortic diastolic murmur, but the diastolic pressure remained normal and there was a good cardiac output. The patient's postoperative course was without complication and she now pursues a normal life.

Comment. This is an instance of a coronary sinus aneurysm complicated by bacterial endocarditis and associated with an interventricular septal defect. A fistula was discovered in 1949 when she was explored for a patent ductus arteriosus. The calcification in the aortic valve was probably related to turbulence from the fistula.

CASE III. O. B., a thirty-four year old white man was said to have had a murmur at fourteen years of age. He was essentially asymptomatic until he was thirty years old. He was hiking at an altitude of 8,500 feet and noted moderately severe dyspnea; whereas, at sea level, he was able to run, swim, hike and fish without having any symptoms. In the year and a half before admission, he noted occasional tachycardia while sitting quietly, and occasionally was bothered by a forceful cardiac impulse while trying to go to sleep at night. For six years he was aware of a continuous "noise" in his chest. On examination, his blood pressure was 132/52 mm. Hg and his pulse rate was 80 per minute. The heart was obviously enlarged with the point of maximum impulse in the sixth intercostal space in the mid-clavicular line. There was a continuous thrill in the third and fourth intercostal spaces to the left of the sternum. Along the right sternal border there was a blowing insufficiency-type diastolic murmur which was loudest in the second intercostal space. At the fourth intercostal space to the left of the sternum, there was a grade 6 continuous machinery murmur with the diastolic component the loudest and the longest. The liver was not palpable and there was no pretibial edema. There was no distention or pulsations of the neck veins.

He was admitted to another hospital for evaluation. Electrocardiograms showed borderline left ventricular hypertrophy. Cardiac fluoroscopy showed left ventricular enlargement, one plus right ventricular enlargement and a pulmonary artery segment which was prominent and pulsated vigorously. Because of the location and character of the murmur, catheterization into the right side of the heart was carried out. The catheter was passed down a persistent left superior vena cava into the coronary sinus. Blood samples were obtained and pressure measurements were made in the right atrium and right ventricle. It was not possible to catheterize the pulmonary artery so the catheter was removed and inserted into the right basilic vein. Again the catheter passed into the coronary sinus and back out through the persistent left superior vena cava. It would not enter the pulmonary artery. See Table III for data concerning catheterization. It was their belief that the catheterization demonstrated an increase in oxygen saturation between the right atrium and right ventricle and that this could represent either a ventricular septal defect, a ruptured sinus of Valsalva aneurysm into the right ventricle or a patent ductus arteriosus with pulmonary insufficiency. A retrograde aortogram was obtained showing a moderately good opacification of the ascending aorta and simultaneously, the pulmonary artery. This was interpreted as showing an extremely large ductus (2 cm.) and regurgitation of contrast substance into the right ventricle through what was assumed to be the pulmonary artery.

An exploratory operation was performed on the presumptive diagnosis of patent ductus arteriosus and pulmonary insufficiency. A small ligamentum was identified with no thrill in it. Palpation over the entire precordium revealed an extremely

TABLE III
CARDIAC CATHETERIZATION DATA (CASE III)

Catheter Position	Oxygen Content (Van Slyke) (volumes %)	Blood Pressure (mm. Hg)
Coronary sinus	...	18/3 (5 mean)
Coronary sinus, wedge	15.3	54/40
Superior vena cava		
Left	...	10 (mean)
Right	12.9	.....
Inferior vena cava	13.6	12 (mean)
Right atrium		
Low	12.8	.....
Mid	12.6	5 (mean)
High	12.4	.....
Right ventricle		
Apex	16.7	100/15
High	16.0	100/15
Low	15.4	100/15
Brachial artery	17.2	165/50
Pulmonary artery	89.2*	38/15 (26 mean)*
Aorta	96.2*	95/45 (65 mean)*
Left superior vena cava	89.2*	.....*

* At time of exploration for patent ductus arteriosus.

coarse continuous thrill over the base of the aorta. Blood pressures were determined and oxygen samples taken from the aorta and the pulmonary artery. The diagnosis at surgery was ruptured aneurysm of the sinus of Valsalva into the right ventricle. The patient's postoperative course was without complication.

The patient returned to work and carried out his duties well. He was admitted to the Cardiovascular Unit of the Presbyterian Medical Center in October 1960. The history and examination were as noted previously. An electrocardiogram was interpreted as showing left ventricular hypertrophy and left atrial preponderance. This was confirmed by a vectorcardiogram. Fluoroscopy and cardiac x-ray films showed enlargement of both the right chambers, the left ventricle and probably the left atrium. The main pulmonary artery was markedly enlarged with vigorous pulsations. The pulmonary vessels were considerably engorged and there was a conspicuous hilar dance. The aorta was not unusually prominent, but there were vigorous aortic pulsations especially in the ascending aorta.

Surgery with the aid of extracorporeal circulation and hypothermia was performed. Through a transverse right ventriculotomy, the "windsock-like" aneurysmal sac was identified with several 3 to 4 mm. openings in the end, and just beneath it there was a 5 mm. ventricular septal defect. The aneurysm was excised and the fistulous opening and the ventricular septal defect were separately closed with interrupted sutures. A Dacron patch was then sutured over the repair. A patent foramen ovale was closed through a right atriotomy. The patient's postoperative course was without complication.

COMMENTS

Mall, in 1912 [*12,13*], and Abbott [*14*], in 1919, called attention to the embryonic defect. This has generally been accepted as a lack of or faulty fusion of the distal and proximal bulbar swellings, the future pulmonary and aortic valves, resulting in a congenital fistula or weakness above the aortic valve ring and below the pulmonary valve ring. This defect occurs in the right half of the aorta so that the right coronary cusp or adjacent two-thirds of the noncoronary cusp may be involved.

Venning [*15*] gave credit to C. V. Harrison for suggesting that the fundamental defect was a defective development of the elastic tissue at the base of the aorta, occurring at a later date than the fusion of the bulbar swellings. If this view is correct, then the pressure differences between the aortic root and the right side of the heart account to some extent for the high incidence of rupture in this area. The angiocardiographic findings by Steinberg [*16*] of six congenital unruptured aneurysms of the aortic sinuses among 128 patients with coarctation of the aorta would tend to support this theory. There is also a high incidence of this anomaly in Marfan's syndrome [*17*]. On the other hand, more aneurysms rupture into the right ventricle than the right atrium and there is an associated ventricular septal defect in 25 to 50 per cent of the cases which rupture into the ventricle. Morgan Jones and Langley collected five cases and Kjellberg and associates [*18*] had two others with congenital fistula without prior aneurysm formation.

The anatomic defect is a lack of continuity of the media of the aorta and the annulus fibrosis of the aortic valve ring. This definitive work was carried out by Edwards, Burchell and Christensen [*19,20*]. (Fig. 3.)

Morgan Jones and Langley reported fifteen anomalies of the aortic cusps in their twenty-five cases of congenital aneurysms. Two of the patients had coarctation of the aorta and one had pulmonary conus stenosis. Four cases were associated with aortic incompetence. Ten patients had ventricular septal defects.

Sawyers, Adams and Scott reviewed all the cases they were able to find since Thurnam's original description. Of the forty-seven cases reviewed, forty-five were confirmed at autopsy. The aneurysm arose from the right coronary sinus in thirty-four instances, from the noncoronary sinus in thirteen and from the left coronary sinus in two. Rupture of the aneurysm had occurred in thirty-seven of the autopsied patients. Twenty-six (70 per cent) of the ruptured aneurysms arose from the right coronary sinus, eleven (30 per cent) from the noncoronary sinus. Rupture had not occurred in either of the two aneurysms arising from the left coronary sinus. Of the twenty-six ruptured aneurysms of the right coronary sinus, nineteen (70 per cent) terminated in the right ventricle, three in the right atrium. All eleven arising from the noncoronary sinus ruptured into the right atrium. Eighty-two per cent were men and 70 per cent had no symptoms prior to rupture. The characteristic loud, harsh or shrill continuous murmur was present in 94 per cent of the cases. It was usually best heard in the third and fourth interspaces. The survival time after rupture was approximately one year if two patients,

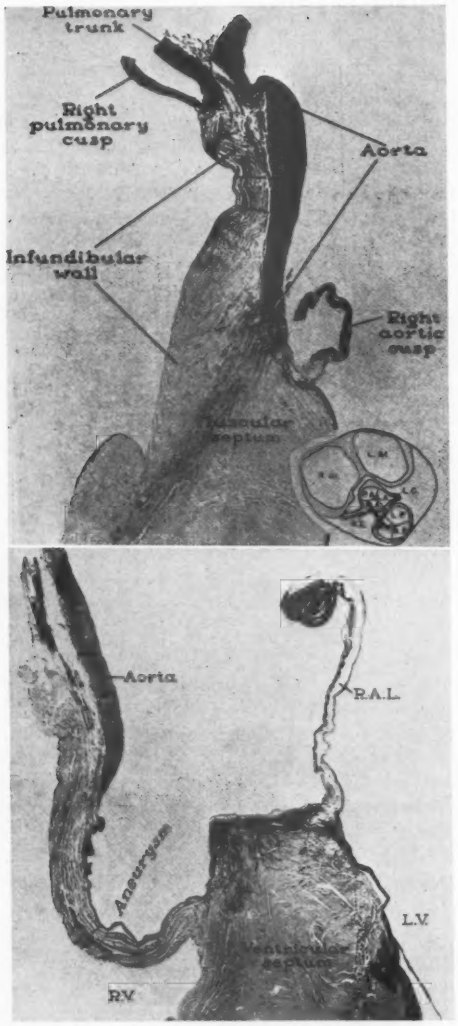

FIG. 3. A, the normal anatomy of the aortic root as seen in a section through the right coronary sinus is depicted. B, shows the basic defect as the lack of continuity of the media of the aortic wall with the annulus fibrosis of the aortic valve ring. A small aneurysm has formed. (From: EDWARDS, J. E. and BURCHELL, H. D. *Thorax*, 12: 125, 1957 [20].)

who lived ten and fifteen years, were excluded from the series.

Because our patients had a much more benign course and particularly because of the rapid advances in open heart surgery, we decided it would be worthwhile to examine the cases reported since the review by Sawyers, Adams and Scott [4]. We have limited this to a review of cases of ruptured congenital aortic sinus aneurysms which were reported with sufficient detail in the English literature. We found a total of twenty-nine cases in addition to our three cases [5–11,18,21,23–26,28–32].

Fifteen of the patients were of the male sex and seventen were of the female sex. The average age at the time of rupture of the aneurysm was nineteen years. The average life span after rupture until operation or death was four and a half years. Thirteen of the patients who had evidence of an aneurysmal sac had murmurs before rupture occurred. Of these thirteen, eight had a ventricular septal defect. In the case reported by Brown and co-workers [21], there was a continuous murmur in the fourth left interspace for eight years before rupture was thought to have occurred. Falholt and Thomsen [22] described a continuous murmur and thrill in the second and third intercostal spaces to the left of the sternum in a patient with unruptured aneurysm of an aortic sinus. The aneurysm was demonstrated by angiocardiogram and was proved not to have a fistula or shunt by cardiac catheterization. They believed that the continuous murmur could be explained by blood flowing into the aneurysm during diastole and being forced out by the contraction of the heart in systole. Others have postulated distortion of the pulmonary outflow tract or of the aortic, pulmonary or tricuspid valve by the aneurysmal sac as the cause of murmurs occurring before rupture. Also it may be that some diastolic murmurs are caused by minute perforations in the wall of the aneurysm.

After rupture, twenty-eight of the patients had a continuous murmur. Kay's patient, in whom the fistula had dissected into the wall of the left atrium with resultant multiple small fistulous openings into the left atrium, had no murmur [9]. Systolic and diastolic murmurs only were heard in one patient of Davidsen's [27] and in our patient (Case 1) with infundibular pulmonic stenosis; a systolic murmur only was heard in one patient with tetralogy of Fallot with a fistula from the right coronary sinus to the right ventricle [11].

The characteristic murmur was continuous, loud and superficial. It was described by Abbott [33] as having a diastolic accentuation. This additional characteristic was mentioned only infrequently. Our second patient (Case 11) had

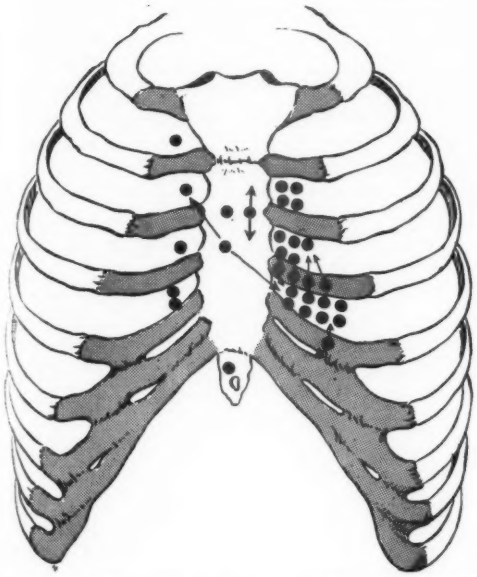

FIG. 4. A diagram showing the position of maximal intensity of the murmurs in the thirty-two cases reviewed.

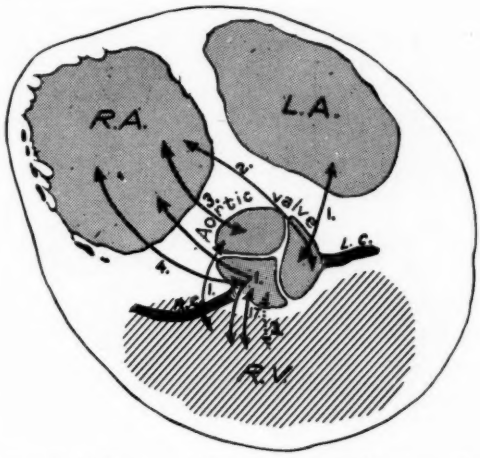

FIG. 5. A diagram of the heart sectioned horizontally immediately above the aortic valve and below the pulmonary valve. The heavy lines represent the number of aorticocardiac fistula known to have arisen in the respective coronary sinuses and to have terminated in the respective chambers. The dotted line represents three fistulas probably arising in the right coronary sinus.

a diastolic murmur which was decrescendo in character; our third patient (Case III) had a diastolic murmur which was crescendo in character. The murmur was loudest in the third or fourth intercostal space to the left of the sternum nineteen times, in the second left intercostal space four times, twice in the fourth right intercostal space, once in the third right space, once in the second right and fourth left space, once in the second right space, once in the first right space, once midsternally at the third rib and once over the xphoid. (Fig. 4.) Five of the patients with an atypical location of the murmur had shunts to the right atrium. This location of the murmur to the right of the sternum in shunts to the right atrium was previously commented on by Herrmann and Schofield [*34*].

Of the thirty-two cases, seventeen fistulas were definitely known to originate in the right coronary sinus and terminate in the right ventricle, an additional three probably originated there and terminated in the right ventricle. Four originated in the right coronary sinus and terminated in the right atrium, and one originated in the right coronary sinus and terminated in both the right atrium and right ventricle. Three were from the noncoronary sinus to the right atrium, and one from the noncoronary sinus to the right ventricle. One originated from the left coronary sinus and terminated in the left atrium, two arose from the left coronary sinus and terminated in the right atrium. (Fig. 5.)

These latter three are unique, for although there have been several unruptured aneurysms of the left coronary sinus previously reported [*35*], none had ruptured to form an aorticocardiac fistula. One of these arising from the left coronary sinus was reported by Kay. The origin was not definitely identified by opening the aorta. It could conceivably have been from the noncoronary sinus but the position of the intramural hematoma on the anterior wall of the left atrium makes this unlikely. The origin of the fistula in one of Spencer, Blake and Bahnson's patients was, of course, discussed extensively by them. They cited Edwards and Burchell [*20*], who mentioned the possibility of an accessory left coronary artery with aneurysmal dilatation and communication with the right atrium. They believed they could not exclude this possibility, but because of the typical appearance of the aortic opening in the base of the coronary sinus they favored the diagnosis of aneurysm of the sinus of

Valsalva. Kieffer and Winchell recently added to the literature from the University of Minneapolis Hospitals seven more instances of congenital ruptured aneurysms. One of the autopsy cases was found to have a fistulous tract from the left coronary cusp to the right atrium.

In eight of the thirty-two cases there was a coexistent ventricular septal defect. Ten patients had another anomaly in addition: four had aortic valvular insufficiency, one had a bicuspid aortic valve and two had infundibular pulmonic stenosis. One had an associated mild coarctation of the aorta in addition to a ventricular septal defect and one was associated with a tetralogy of Fallot. One other had a large noncoronary cusp of the aortic valve.

Forty-five per cent of these patients had an acute onset of symptoms. Sudden pain in the chest heralded the onset in 26 per cent and sudden pain in the right upper quadrant was the sign in 10 per cent. Dyspnea was present early in 60 per cent. Weakness and fatigability were present in 25 per cent of the cases as very early symptoms. Angina was present in two cases. Three patients were asymptomatic.

PATHOLOGIC PHYSIOLOGY AND DIFFERENTIAL DIAGNOSIS

The aorticocardiac fistula is from the high pressure aortic root to the relatively low pressure right ventricle or low pressure right atrium. The resultant shunt is left to right with a flow depending on the size of the fistula. There is usually a large runoff from the aorta to the right ventricle in diastole and to the right atrium throughout the entire cardiac cycle. The pulmonary flow is increased; some have temporary left-sided failure, to a varying degree. The systemic diastolic pressure is low, the systemic systolic pressure increases. The work load of the heart increases in the face of a decrease in the effective coronary circulation due to a low diastolic pressure. Usually the right heart fails first and the patient dies in marked congestive failure. The combination of tricuspid and aortic incompetence is highly suggestive of this lesion.

The pathologic physiology is of course similar to that of patent ductus arteriosus, aorticopulmonary window, fistula from an aberrant coronary artery to the right atrium, right ventricle or pulmonary artery, and high ventricular septal defect with aortic regurgitation. In the first two, there is a pulmonary valve to protect the right heart from the full force of the systemic pressure and protection especially from diastolic overloading [*36*].

The diagnosis of sinus of Valsalva fistula can be highly suspect in the patient who is relatively young, has been in good health, has had no cardiac murmur and then suddenly has an episode of pain in his chest, dyspnea and discomfort in the right upper quadrant accompanied by a continuous murmur. He may rapidly go into right-sided heart failure. The diagnosis should also be highly suspected in patients who have had a murmur but not many symptoms, who develop similar complaints and whose murmur suddenly becomes continuous. It is also highly suspect if a preexisting murmur becomes continuous after a bout of bacterial endocarditis, or if bacterial endocarditis develops in a heart previously considered normal [*2*]. Five cases in this series had bacterial endocarditis. This has been thought to be secondary in all cases.

Examination will usually show a hyperactive heart with enlargement to the left and a right ventricular heave. A thrill is frequently present, and the murmur, as previously noted, is frequently but not always characteristic. Its point of maximum intensity, and to some extent its character, is related to the site of origin of the fistula and to the site of termination as well as to coexisting defects.

The pain and discomfort frequently subside and there is usually a varying period of relative compensation followed by progressive decompensation. There is, at first, partial response to digitalization, salt restriction and diuretics, but this is followed by progressive failure.

Other aids to the diagnosis include a roentgenogram which usually shows generalized cardiac enlargement with prominent pulmonary vascularity. If the shunt is large, there may be marked cardiac enlargement affecting all chambers with pulmonary vascular engorgement and pulsations. (Fig. 6.) The aorta may be smaller than that seen in a patient with patent ductus arteriosus [*11,18*]. The electrocardiogram is variable. Seven patients had normal or essentially normal electrocardiograms, three had complete right bundle branch block with left ventricular hypertrophy and strain, six had left ventricular strain, five had left ventricular hypertrophy, five had combined hypertrophy, one had right ventricular hypertrophy, one had right axis deviation and one had right

bundle branch block. The electrocardiogram was not described in the other cases. Several cases [37–39] have been reported in which there was heart block caused by pressure of the aneurysm on the conduction mechanism.

Dye dilution curves may prove helpful [28]. Angiocardiograms and retrograde aortograms may be diagnostic but have been more reliable in demonstrating aneurysms before rupture. Cardiac catheterization is of definite value in the large majority of patients who have aorticocardiac fistulas to the right side of the heart. There will be a left to right shunt to the right atrium or right ventricle. The oxygen saturation will show a step-up and there will usually be an increase in the pressures. There might be some difficulty, however, in differentiating these fistulas by catheterization data from a patient with patent ductus arteriosus in the presence of pulmonary valvular insufficiency or with a coexistent ventricular septal defect.

FIG. 6. The roentgenogram of the chest of Case III showing generalized enlargement of the heart and increased pulmonary vascularity.

SURGICAL CORRECTION

The history of treatment has progressed from supportive medical therapy to complete open heart repair. It has included the use of a Hufnagel valve in the descending aorta [40], attempts to perform a circumclusion operation [23], ligation or occlusion of the aneurysm sac using temporary inflow occlusion and hypothermia [21] or the atrial well technic [41], occlusion of the fistula with a prosthetic tube using temporary venous occlusion [5], suture of the defect under hypothermia to complete occlusion of the fistula and reconstruction of the aortic root using extracorporeal circulation alone or combined with hypothermia.

Sixteen of the nineteen patients operated on using hypothermia (three cases) or extracorporeal support (sixteen cases) are living and well. Four patients of the successful cases, including our second case, had some mild degree of aortic insufficiency postoperatively [6,8,29].

Extracorporeal circulation is necessary to give the surgeon sufficient time to assess the situation, close the fistula and suture a Dacron or Teflon® patch between the aorta and the aortic valve ring as well as close a ventricular septal defect if this is present. The additional use of hypothermia with extracorporeal circulation gives the added advantage of minimizing myocardial damage if the aorta has to be opened to correct an associated prolapsed valve cusp or close the fistula on the aortic side if the fistulous tract is a long one.

SUMMARY

The basic defect of a congenital aneurysm of the aortic sinuses of Valsalva is a lack of continuity between the media of the aorta and the annulus fibrosus of the aortic valve ring. Most of the aneurysms arise in the right and noncoronary cusps and rupture into the right ventricle or right atrium.

Rupture of the aneurysm leads to an aorticocardiac fistula which overloads the right heart leading to severe congestive failure. The murmur is usually continuous, loud and superficial and most frequently heard best in the third and fourth intercostal spaces to the left of the sternum.

These fistulas and associated defects can be corrected with open heart surgery with a low mortality rate.

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DISCUSSION

Emile F. Holman (San Francisco, Calif.): It is a pleasure, indeed, to discuss this fascinating report

on an operation which the authors now execute with such consummate ease, but which only a short time ago appeared utterly impossible. I remember well a young woman twenty-six years old and mother of three children, known to have a cardiac murmur since infancy, who had experienced three pregnancies without difficulty. In her fourth pregnancy, however, she had the following complications: dyspnea, generalized edema and recurring episodes of fever.

When admitted to Stanford Hospital she was totally decompensated; she had a high fever, positive blood cultures, an exquisite thrill and a continuous murmur with systolic intensification over the base of the heart. On the basis of a possible patent ductus with complicating endarteritis and endocarditis, an exploratory thoracotomy was performed which disclosed no ductus but an extremely large pulmonary artery and a thrill with maximum murmur at the origin of the aorta and pulmonary artery.

With the equipment available at that time, an operation was impossible. She died seven days later. Autopsy revealed a high interventricular septal defect and a ruptured aneurysm of the sinus of Valsalva into the right ventricle.

When I view the truly remarkable achievements made possible by open heart surgery, I am always tempted to muse upon the great pleasure some of the master surgeons of the past would have found in the almost daily performance in surgical clinics the world over of these astounding miracles.

I should like to dwell for a brief moment on the pathologic physiology associated with rupture of an aneurysm of the sinus of Valsalva into the right ventricle. This constitutes an arteriovenous shunt from a high pressure area to a low pressure area, resulting in the diversion of a considerable volume of the circulating blood from the peripheral arterial system into the pulmonary circuit. Depending on the size of the abnormal communication, there is a drop in the arterial pressure of greater or less degree. The immediate compensatory response is an increase in total circulating blood volume.

Since the resistance to flow is less in the pulmonary circuit than in the systemic circuit, there will be a tendency for more and more blood to be sequestrated in the pulmonary circuit, with a concomitant dilatation of all the structures included in the shorter circuit; namely, the right ventricle, pulmonary artery and vein, left auricle and left ventricle and the fistulous opening itself. The resulting vicious circle can only end in cardiac overdilatation and decompensation.

It would be most interesting when such cases are encountered to determine both the total blood volume and the cardiac output. The great importance of total blood mass as a physiologic and pathologic variable is just beginning to be fully appreciated, and careful studies of these variations are of great clinical and academic interest.

One bit of indirect evidence in Case II was the increase in peripheral blood pressure when the communication was closed; this was in small part due to the elimination of the site of decreased resistance to flow, but in large part to the increased bulk of blood being directed into the systemic circulation. The reduction in the size of the heart following elimination of the offending abnormal opening is also easily demonstrable. Such detailed studies add greatly to our fundamental understanding of the pathologic physiology involved in these abnormal shunts.

FRANK GERBODE (closing): I would like to thank Dr. Holman for his kind and astute remarks. I would like to make three points about this lesion which is of interest to me. (1) All three of these patients were adults who were cardiac cripples. They had been sick for a long time, yet when the fistula was closed they returned to normal physical activity. This is important because the shunt itself apparently does not have a lasting deleterious effect on the circulatory system, and if it can be closed successfully the patients are returned to normal activity.

(2) The murmur, although continuous and associated with a wide pulse pressure, is a very superficial murmur. The shunt is usually toward the anterior wall of the right ventricle, so the murmur feels as though it is directly under the skin. I believe this is important from the point of view of physical examination.

(3) The third point is one which Dr. Holman made experimentally some time ago when he was studying fistulas. He postulated that any sort of connection between a high and low pressure area in the circulatory system would have a similar physiologic effect. He produced in animals interventricular septal defects, and postulated that on closing such a defect the blood pressure would rise and the pulse would slow. We have confirmed this in the beating human heart by closing defects digitally.

As you all know, if one shuts off a patent ductus or an acquired arteriovenous fistula, there is a slowing of the pulse. This is called Branham's bradycardiac phenomenon. There is also a rise in the diastolic pressure and a rise in the systolic pressure at the same time. It is interesting that we found this same bradycardia effect on closing a left ventricle-right atrial shunt digitally with the heart beating.

Experiences with the Open Correction of Acquired Mitral Valvular Disease, with Special Reference to Insufficiency

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Many reports are now in the literature concerning the correction of mitral regurgitation by open methods [1–8]. Most investigators give support to the thesis that regurgitation is correctable by annuloplasty, yet they qualify any enthusiasm with certain reservations. There is general agreement that annuloplasty is not applicable to all patients with mitral regurgitation; also, there seems to be general agreement that alternative procedures are less apt to be successful in most instances. Some question the long term results in patients surviving annuloplasty. Others are uncertain in their choice of patients for surgery.

Despite the fact that open operations for mitral regurgitation have been performed since the middle of 1956, there have been relatively few performed. Recently we summarized our surgical experience and reviewed survivors of the open operation in order to evaluate our position. The purpose of this presentation is to report the results of this study.

PRESENT SERIES

From September 19, 1956 to January 12, 1961, thirty-three patients have been operated on for mitral regurgitation and/or stenosis. Often the patient exhibited, in addition, hemodynamic lesions at other valves; however, the predominant reason for the patient's disability was thought to be related to the mitral lesion. No case has been excluded for any reason. This series differs from many reported series in that no Class II (NYHA)* patients have been operated on. The number of patients in Classes III and IV were almost numerically equal.

From the surgical viewpoint, it became apparent in order to make a meaningful evaluation, that the cases should be analyzed as follows: (1) pure mitral stenosis; (2) pure mitral regurgitation; (3) mixed mitral stenosis and mitral regurgitation; and (4) mitral regurgitation and/or mitral stenosis with aortic insufficiency. While these divisions may seem artificial, the separation of all patients with either organic or functional aortic insufficiency is justified for reasons previously described [4]. There can be little doubt that the patient with associated though minor aortic insufficiency has a serious operative prognosis when open surgery on the mitral valve is performed.

The number of patients with pure mitral stenosis operated on by the open approach have been few. (Table I.) Originally, it was believed that open mitral commissurotomy was indicated in (1) patients previously operated on by closed methods with either restenosis or an unsatisfactory commissurotomy at the initial operation and (2) patients with one or more systemic embolic episodes. These indications for the open approach changed rapidly for the following reasons: in one patient with seven previous systemic embolic episodes and in another patient with five previous systemic embolic episodes, no left atrial clot was seen at open operation; in both patients, only clean glistening endocardium was present. Because

* New York Heart Association.

TABLE I

OPEN HEART SURGERY FOR PURE MITRAL STENOSIS

Case No.	Age (yr.)	NYHA Classification	Comment	Survived*
1(G. T.)	54	IV	Large left atrial clot	Yes
2(L. T.)	55	III	Previous blind commissurotomy without satisfactory result; large, left atrial clot	Yes
3(L. L.)	47	III	Diagnosed mitral regurgitation; pure mitral stenosis found	Yes

* Survivors = 3; deaths = 0.

of these experiences, this indication for the open approach was thought to be invalid.

Open commissurotomy has been performed on patients with pure stenosis and those with mixed lesions. The difficulty in determining the commissures during our early experience was found to be greatly assisted by beginning the commissurotomy by forcibly expanding Péan's forceps in the orifice. Because this worked so well, in subsequent patients with the valve under direct vision the transventricular dilator was placed in the stenotic orifice and opened. It became obvious that when optimum use was made of the dilator, no further improvement was possible even with the valve under direct vision. On the basis of these experiences, it did not seem rational to use the full-dress open approach to correct mitral stenosis with an instrument which was designed for the blind approach. This accounts for the small number of open mitral commissurotomies performed in this series. At present, we do not advise the open approach for a second mitral commissurotomy or in patients with previous

TABLE II

OPEN HEART SURGERY FOR PURE MITRAL INSUFFICIENCY*

Case No.	Age (yr.)	NYHA Classification	Comment	Survived*
1(L. F.)	32	IV	Air embolism; no residual	Yes
2(J. C.)	23	III	Died six hours postoperatively, progressive hypotension	No
3(I. C.)	30	III	...	Yes
4(R. D.)	36	III	...	Yes
5(A. F.)	49	III	Previously operated on for pure mitral stenosis; mitral insufficiency created by poorly placed commissurotomy; repair of valve and commissurotomy	Yes
6(L. M.)	26	IV	...	Yes
7(E. A.)	21	III	...	Yes
8(G. F.)	19	III	...	Yes
9(M. E.)	40	III	...	Yes
10(M. G.)	44	IV	...	Yes
11 (J. D.)	45	IV	Air embolism (minor)	Yes

* Survivors = 10; deaths = 1.

TABLE III

OPEN HEART SURGERY FOR MIXED MITRAL STENOSIS AND MITRAL INSUFFICIENCY*

Case No.	Age (yr.)	NYHA Classification	Procedure†	Comment	Survived‡
1(E. W.)	50	IV	ALC PMA	Congestive heart failure; associated tricuspid insufficiency, hypertension, hemiplegia, severe causalgia	No
2(H. E.)	39	IV	ALC PMA	Calcific valve	Yes
3(R. K.)	43	IV	ALC PMA	Calcific valve; myocardial infarct postoperatively	Yes
4(L. R.)	44	IV	ALC PMA Ivalon roll, extracardiac	Calcific valve; improvised repair	No
5(J. R.)	48	III	ALC Ivalon roll, extracardiac	Calcific valve	Yes
6(M. C.)	45	III	ALC Ivalon roll, extracardiac	Calcific valve; calcific embolus to left coronary artery with ventricular fibrillation	No
7(B. H.)	38	III	ALC PMC	Calcific valve	Yes

* Predominance is questionable.

† ALC = anterolateral commissurotomy, PMA = posteromedial annuloplasty.

‡ Survivors = 4; deaths = 3.

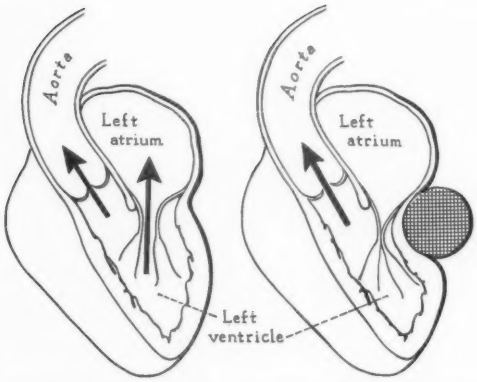
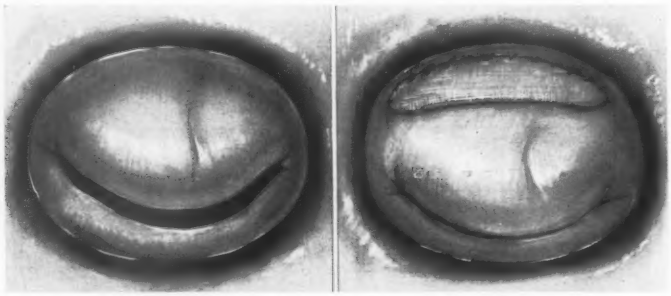


FIG. 1. In four patients, a compressed (10:1) Ivalon® roll 4 cm. in diameter was placed transversely across the posterior left ventricle in the hope that the posterior wall would be pushed forward sufficiently to aid approximation of the posterior mitral leaflet with the aortic and reducing regurgitation during ventricular systole. The effect of position on regurgitation was checked by the intracardiac finger. While the degree of regurgitation seemed less, the betterment produced was unsatisfactory.

systemic embolization. Furthermore, the more frequent utilization of transatrial or transventricular dilating instruments at the initial operation will result in even better results than were possible with the older cutting instruments. Our only indication for the open approach for pure mitral stenosis would be in a previously well documented instance of subvalvular stenosis which might limit the value of a transventricular dilatation. Of course, if a satisfactory prosthetic mitral valve were available, the open approach might be more frequently used.

When pure mitral insufficiency exists, the survival rate is good. The improvement in these patients is impressive and sustained as will be pointed out subsequently. (Table II.) Frequently it is stated that posteromedial annuloplasty is of value only in patients exhibiting a dilated annulus. This has not been our experience. Patients with what appear to be normal-sized atrioventricular canals have had massive mitral regurgitation totally corrected with a well placed single suture. At least one additional suture and often two were used to lessen the pull on a single suture; but for the correction of the regurgitation itself, only a single stitch was required. The surgical technic has been previously described [4] and will not be reiterated here except to mention that No. 2 interrupted silk sutures are used. These are tied down snugly. The knots are buried by an additional row of No. 3–0 silk sutures approximating the atrial wall above the annuloplasty. No sutures other than in the posteromedial area have been used. Care is taken to avoid



A B

FIG. 2. In two patients, an attempt was made to increase the cross sectional area of the valve by the utilization of prosthetic material (Ivalon,® 10:1; Teflon,® woven). The valves in both patients were deformed by calcification (A). It was hoped that by the insertion of the prosthetic material, the free edge of the aortic leaflet would be pushed backwards with a ballooning effect as the chordal attachments pulled downward the free edge of the leaflet allowing abutment with the posterior leaflet during systole (B). Unfortunately, these badly deformed valves did not behave in this fashion; the only ballooning effect tended to occur in the prosthetic substitute. This principle of increasing the valvular cross sectional area would appear to have merit mainly for those patients with mobile valves in which posteromedial annuloplasty is eminently satisfactory.

TABLE IV

OPEN HEART SURGERY FOR MITRAL INSUFFICIENCY AND/OR MITRAL STENOSIS WITH AORTIC INSUFFICIENCY

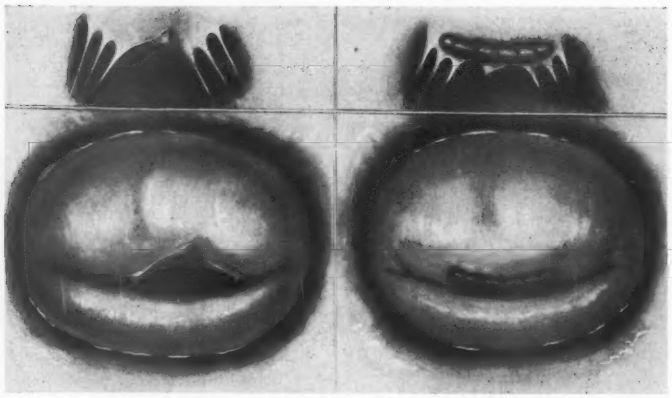
Case No.	Age (yr.)	NYHA Classification	Lesion*	Comment	Survived†
1(M. H.)	23	IV	Pure MI; massive AI	Ventricular fibrillation; death on operating table	No
2(C. W.)	42	IV	MS and MR; massive AI; functional origin(?)	Ventricular fibrillation; death on operating table	No
3(M. W.)	31	III	Pure MS; massive AI; functional origin(?)	Left ventricular overload; arrest; fibrillation; death on operating table previous leg amputation for embolus; seven previous episodes	No
4(W. M.)	45	IV	Pure MR; associated TI and AI	Arterial cannula fell out; ventricular fibrillation; death on operating table	No
5(B. C.)	31	III	MS and MR; massive AI; ventricular fibrillation with hypothermia	Died on eighth postoperative day of massive gastrointestinal bleeding; never regained consciousness	No
6(E. H.)	49	III	MS, MR, AS, AI	Previous blind commissurotomy, unsatisfactory result	Yes
7(B. R.)	46	III	MR (ruptured chordae); AI; functional origin(?)	Unsatisfactory repair	No
8(A. Q.)	44	IV	MS, MR, AI	.....	Yes
9(F. O.)	44	III	MS and MR; AI	.....	Yes
10(C. O.)	31	IV	MS, MR, TI, AI	Attempted correction of aortic insufficiency and mitral insufficiency (transseptal); death on operating table	No
11(F. C.)	31	III	MS and AI	Previous blind commissurotomy five years before; large atrial clots; iatrogenic dissecting aneurysm; death on operating table	No
12(D. R.)	49	IV	MR and MS; TI and AI	Previously rejected for surgery; hemiplegia; improvised repair with Ivalon valvular replacement; death on operating table	No

* MI = mitral insufficiency; AI = aortic insufficiency; MS = mitral stenosis; MR = mitral regurgitation; TI = tricuspid insufficiency

† Survivors = 3; deaths = 9.

producing mitral stenosis. Only silk sutures are used to approximate the annulus. No buttressing material has been used.

In Table III are data for those patients with mitral stenosis with regurgitation. Both lesions contributed to the patients' disability but the major hemodynamic abnormality was believed to be regurgitation. Obviously, the risk for the patient has been great. It is in this group that annuloplasty is frequently impossible to perform. Whether it is possible will be dependent upon the happenstance distribution of calcium. If the valve is calcified in the posteromedial area, the annulus is often "invaded" with calcium and this structure does not retain its normal toughness. Furthermore, it is impossible to approximate the annulus as the calcium is interposed. If the calcium is not sufficiently thickened to be shelf-like and if the deposits are away from the posteromedial area, it is possible to perform on occasion a posteromedial annuloplasty. However, if great deformity is present, the edges of the valves are scalloped and the result is imperfect. Because of the patient's inability to utilize annuloplasty in such situations and because the general condition of the patient in this series was so serious that unless his cardiac status was improved on the table death ensued, the surgeon found himself in the unhappy position of improvising a repair dependent upon the local situation. Figures 1 and 2 indicate the procedures attempted in patients under such circumstances in this group. In addition to the high surgical mortality rate, the survivors did not show significant improvement thereby attesting to the imperfect correction. It is in this group of patients, particularly those with mixed lesions



A B

FIG. 3. Theoretically, the flail area between intact chordae tendineae (A) might be splinted in this fashion (B). Malleable metal has been encased in Teflon. While this method has not been tried clinically, it might have merit with or without posteromedial annuloplasty in the treatment of regurgitation associated with ruptured chordae.

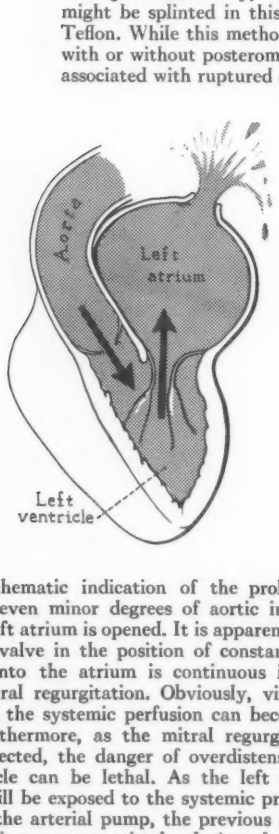


FIG. 4. Schematic indication of the problems generated by even minor degrees of aortic insufficiency when the left atrium is opened. It is apparent that with the aortic valve in the position of constant diastole, the leak into the atrium is continuous in patients having mitral regurgitation. Obviously, vision is obscured and the systemic perfusion can become inadequate. Furthermore, as the mitral regurgitation becomes corrected, the danger of overdistension of the left ventricle can be lethal. As the left ventricular chamber will be exposed to the systemic pressure generated by the arterial pump, the previous decompressure vent (incompetent mitral valve) no longer exists. This sequence of overdistension, leading to ventricular fibrillation, is equally important in open operations on patients with pure mitral stenosis associated with aortic insufficiency.

of stenosis and insufficiency with calcification, that the development of a satisfactory total mitral valve substitute would be the most useful. Furthermore, this group is a potentially large one.

The serious prognosis of open operation on the mitral valve in the presence of associated aortic insufficiency is indicated in Table IV. Within this category there were some patients who were poor candidates for this or any operative procedure; however, at the time the decision was made it seemed reasonable to take an excessive risk since the normal course of the disease results in certain death. In one patient, an unsuccessful attempt was made to correct both aortic insufficiency and mitral insufficiency. Two deaths were attributable to problems of arterial cannulation. In another patient, ruptured chordae tendineae were poorly managed. Recently, McGoon has reported a new method which appears to have merit for most such situations [9]. An untried but possible alternative method was conceived by us. (Fig. 3.) However, the major problems in the patients with associated aortic insufficiency have been (1) our inability to satisfactorily *prevent* the operative area from being obscured by blood, (2) deprivation of the systemic perfusion by this loss and (3) overdistension of the left ventricle as the mitral regurgitation is being corrected. (Fig. 4.) The use of tourniquet occlusion has proven unsatisfactory. It is

impossible to use on the aorta in the adult, because the volume of tissue totally occludes the artery, without the danger of accidental transection. Despite the consideration of many other possible measures to answer this problem, the present method involves periodic occlusion of the aorta by clamp and the use of generalized hypothermia to 30°C. At no time is cardiac arrest considered desirable. These measures are not considered the ultimate but they are the most satisfactory technics we have used.

One disturbing experience has been the unpredicted presence of aortic insufficiency on bypass with absence at autopsy of a deformed aortic valve. This we have termed functional aortic insufficiency. It has been assumed that this is created by the weight of the empty, sagging heart combined with the clockwise rotation of it with the patient in the right lateral position. Supporting the heart by elevation of the pericardium has at times been beneficial in alleviating so called functional aortic insufficiency.

SELECTION OF PATIENTS FOR SURGERY

This series extends back to the earliest experiences with the open management of mitral regurgitation. Some patients, who were considered desperate risks, were offered surgery; these patients, at this time, might be considered nonoperable. By summarizing these experiences (Table v) considerable information has been obtained which should be of value in the future selection of the surgical candidate. It should be noted that the over-all mortality rate (excluding patients with pure mitral stenosis) was 42 per cent. If those patients with associated aortic insufficiency were excluded, the mortality rate was 22 per cent, and, in addition, if those with mixed stenosis and regurgitation were excluded, the mortality rate was 9 per cent. It is obvious that such percentages are meaningless because of the small number of patients involved. However, the significance of these trends cannot be ignored. It is apparent from this experience that if one rejects the patient with associated aortic insufficiency and the patient with mixed stenosis and insufficiency who, roentgenographically, shows evidence of valvular calcification (which is always more extensive at operation than it appears in the x-ray film), then the remaining cases will constitute a select group of patients

TABLE V
MORTALITY SUMMARY OF OPEN HEART SURGERY FOR MITRAL VALVE DISEASE

Lesion	No. of Survivors	No. of Deaths	No. of Patients
Pure MS	3	0	3
Pure MR	10	1	11
Mixed MS and MR	4	3	7
MR and/or MS with AI	3	9	12
Total	20	13	33

in whom posteromedial annuloplasty will be applicable with low risk and excellent opportunity for a good functional result. Unfortunately, the number of patients in this group will not be large and, occasionally, a patient will be denied surgery who could be helped by present methods.

FOLLOW-UP STUDIES

Eleven patients have been re-evaluated clinically, radiologically and by cardiac catherization four to forty months after posteromedial annuloplasty. Nine of these patients have improved significantly, one only slightly and one not at all. The latter patient exhibited both stenosis and regurgitation with a calcified valve. An anterolateral commissurotomy and a posteromedial annuloplasty were performed. Significantly, elevated pressure was present in the pulmonary artery preoperatively which may have represented the presence of fixed vascular changes. Re-evaluation studies for two other patients, who, subjectively, had improved significantly, have not been completed. (Fig. 5.)

Subjective improvement correlated well with the decrease in the severity of mitral regurgitation which was determined by physical examination and tolerance to increased exercise. Of the nine patients who were considered improved at the time of follow-up, six exhibited normal pulmonary arterial and pulmonary capillary pressures. The effective stroke volume increased approximately 20 per cent; the resting arteriovenous oxygen difference was reduced by 15 to 25 per cent, and the heart returned to or almost to its normal size.

The following is a summary of the history and the pre- and postoperative studies on a

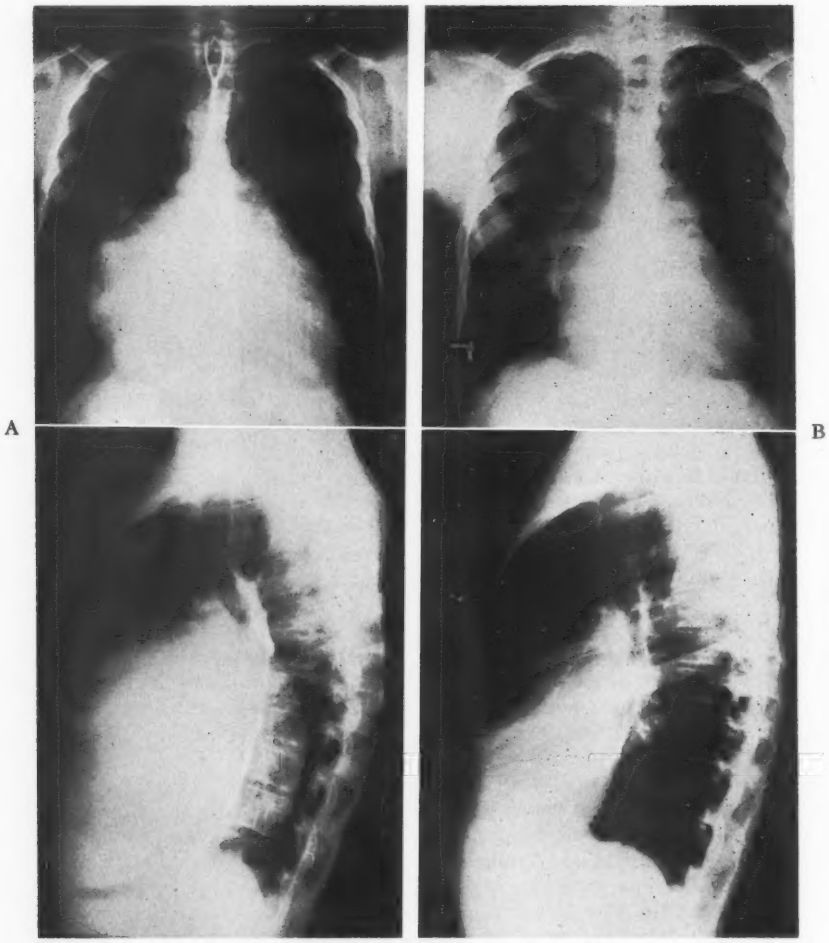


FIG. 5. Pre- (A) and postoperative (B) posterior to anterior and lateral x-ray films of one patient who has not yet been re-evaluated. The postoperative films were taken four months after surgery. The operation was performed almost two years ago. The striking improvement in both the physical and mental status of this patient has been maintained.

patient who has a moderate degree of postoperative residual mitral regurgitation.

J. D. (U.H. No. 033–97), a forty-seven year old housewife, had open heart mitral annuloplasty on May 11, 1960. At twenty-six years of age she had rheumatic fever; treatment constituted bed rest for one year. A heart murmur was noted at that time. For the next seventeen years she had no cardiorespiratory symptoms. Pregnancy at thirty-nine and forty-one years of age was experienced without complication. At forty-five years of age she noticed easy fatigability, weakness and palpitation on exertion. Symptoms were exacerbated by a respiratory infection and progressed during the subsequent nine months. She became unable to manage her housework. A therapeutic program of digitalis, chlorothiazide and dietary sodium chloride restriction did not change her clinical course of progressive disability.

In December 1959, when examined at the University Hospital, she was chronically ill and had moderate elevation of central venous pressure and scattered basilar rales bilaterally which were attributed to low output heart failure. The heart was grossly enlarged with a left ventricular heave prominent at the anterior axillary line. A systolic thrill was palpable at the apex and midaxilla, and a

TABLE VI

EFFECTS OF MITRAL ANNULOPLASTY FOR PATIENT J. D.

Data	Preoperatively	Six Months Postoperatively
Functional capacity	Class IV*	Class II
Heart size		
Left atrium	3+	1+
Left ventricle	2+	Slight dilatation
Mitral regurgitant murmur		
Intensity	Grade 4	Grade 2
Radiation	Left scapula	Mid-axilla
Left ventricular heave	Marked	Absent
Exercise tolerance†		
Endurance	4 minutes	10 minutes
Symptoms	Fatigue and weakness	None
Physical fitness index	3.7	16.9
Hemodynamic data		
Cardiac index (L./minute/m^2)	2.21	3.18
Stroke index (ml./beat/m^2)	31	46
O_2 consumption (cc./minute/m^2)	133.0	138.5
A-V O_2 difference (cc./L.)	60.1	43.6
Pressures (mm. Hg‡)		
Right atrium	$\overline{6.5}$	$\overline{0}$
Right ventricle	40/8	23/1
Pulmonary artery	$\underline{42}/\overline{18}$ $\overline{26}$	$\underline{25}/\overline{10}$ $\overline{18}$
Pulmonary "capillary"	$\overline{20}$	$\overline{10}$
Total pulmonary resistance (dynes sec. $cm.^{-5}$)	683	293
Angiocardiographic data, left ventricle		
End diastolic volume (ml.)	260	156
End systolic volume (ml.)	133	47
Effective stroke volume (ml./beat)	45	71
Regurgitant stroke volume (ml./beat)	82	38
Regurgitant stroke volume (% of total)	64	35

* NYHA classification.

† Treadmill exercise test performed at 1.7 miles per hour at 10 per cent grade. Normal physical fitness index 13 to 26.

‡ Pressures in mm. Hg measured with 0 reference point, 10 cm. anterior to the back.

harsh grade 4/6 pansystolic murmur at the apex radiated around the back. A protodiastolic gallop and a faint early diastolic murmur were also audible at the apex.

The electrocardiogram showed atrial fibrillation and increased QRS voltage suggestive of left ventricular hypertrophy. Enlargement of the left atrium and left ventricle as well as minimal dilatation of the right cardiac chambers were noted in roentgenogram of the chest. The patient's tolerance for walking on a motor-driven treadmill (at 1.7 miles per hour and 10 per cent grade) was markedly reduced to four minutes; the physical fitness index was 3.7 (normal 13 to 26) [*11*].

Hemodynamic data obtained by cardiac catheterization are given in Table VI. Changes in left ventricular volume during systole and diastole, estimated by biplane angiocardiograms, showed dilatation and gross mitral regurgitation. Since end diastolic volume of the left ventricle was 260 ml., the end systolic volume was 133 ml. and the effective stroke volume (by Fick output measurement) was 45 ml. per beat. The regurgitant stroke volume, therefore, was 82 ml. per beat (64 per cent of total left ventricular stroke). Accordingly, the regurgitant flow was 7.05 ml. per minute [*12*].

After posteromedial annuloplasty with extracorporeal circulation was performed, the patient improved. (Fig. 6.) By the sixth month following surgery, she was able to care for her children and manage the housework and usual activities without limitation. In December 1960, the patient went ice skating on several occasions. Recent examination revealed no indication of left ventricular overload, a decrease in intensity and radiation of the mitral systolic murmur and roentgenographically, a considerable decrease in cardiac size. She walked the ten minute exercise period during

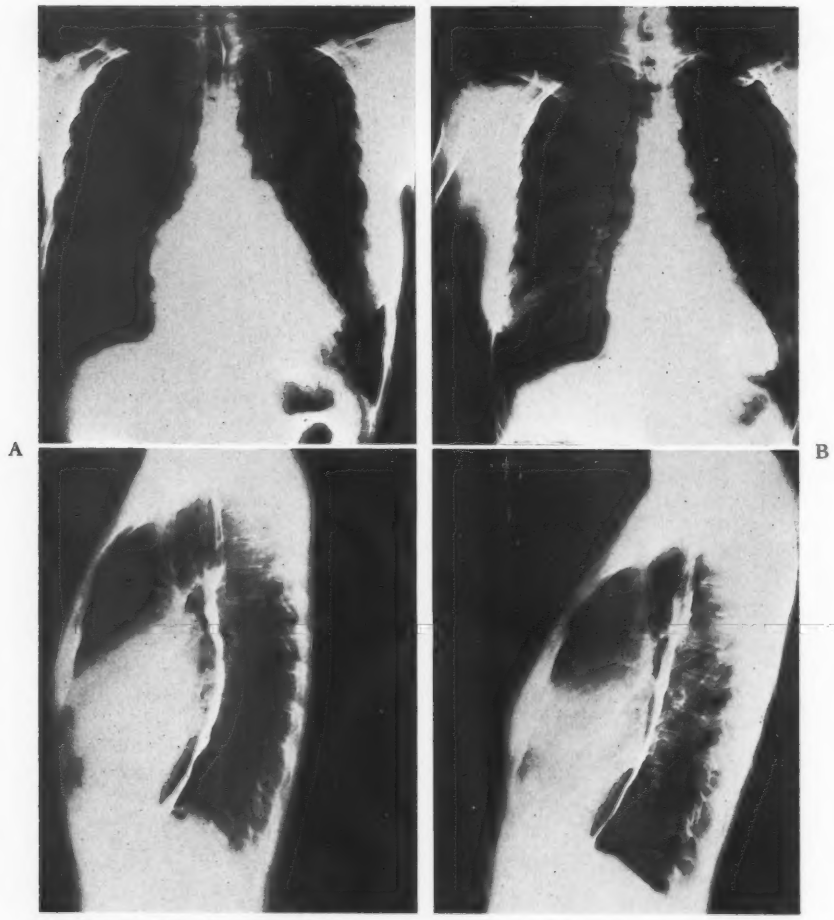


FIG. 6. Pre- (A) and postoperative (B) posteroanterior and lateral x-ray films of J. D. The postoperative roentgenograms were taken on the tenth postoperative day, and already demonstrate reduction in size of the cardiac silhouette.

the same standard exercise test without symptoms, and had a physical fitness score of 16.9. Resting hemodynamic measurements obtained six months after surgery had returned to normal.

Repeat measurements of left ventricular volumes from films, obtained with biplane angiocardiograph, showed a normal end systolic volume of 47 ml. The end diastolic volume of 156 ml. indicated some residual dilatation of the left ventricle and some mitral regurgitation remained, measuring about 35 per cent of total left ventricular stroke volume. The regurgitation present six months after annuloplasty may reflect residual dilatation of the left ventricle from the preoperative overdistension of that chamber. The reduction in mitral regurgitation and return of the hemodynamic measurements to normal following mitral annuloplasty correlated well, in this patient, with the marked decrease in cardiac disability.

COMMENTS

Posteromedial annuloplasty is an operative procedure which has special merit for the correction of acquired mitral regurgitation secondary to rheumatic fever. It is the only operative procedure attempted by us which has produced significant and *lasting* betterment of the patient within the limits of this follow-up period. Unfortunately, like most operative procedures, it is not applicable to all patients.

We are unaware of any procedures of proven equal merit.

The mortality rate in this series has been high. This series represents a learning experience beginning at a time when there were few guide posts regarding the proper patient for treatment and the proper surgical procedure. No patient with the proper hemodynamic lesion was denied surgery. As experience was gained, it became apparent that an excessive mortality accompanied any open operation on the mitral valve in the presence of even minor degrees of aortic insufficiency. Despite this knowledge, open surgery was offered to such patients in the hope that methods could be developed which would reduce the operative risk. While aortic insufficiency can be handled better now, its management is still not completely satisfactory. Furthermore, it has become apparent that the operative risk is excessive for patients with mixed mitral stenosis and regurgitation with x-ray evidence of calcification, and with rare exceptions such patients cannot significantly benefit from any method other than total valvular prosthetic substitution. Some encouraging results regarding the latter have been reported recently by Braunwald et al. [*13*] and Starr [*14*].

While the operative mortality appears excessive, if one excludes those patients with x-ray evidence of calcification and avoids all patients with aortic insufficiency, as has been practiced in other series, the mortality in this series for such selected groups is comparable to others [*5*]. Furthermore, in the present series only patients in Classes III and IV (NYHA) were offered surgery. The number of patients in each of these classes was almost equal. Frequently, patients in Class III were offered surgery when new evidence of progressive deterioration was found which would lead to Class IV status. When surgery is offered to and performed on a significant number of patients in Class II, the survival rate is good regardless of whether the patient derived any benefit from the operative procedure [*6*].

To date the initial improvement of patients who have had posteromedial annuloplasty and been followed for four to forty months has been maintained. No doubt in certain patients some regurgitation persists. Also, we have observed the total disappearance of systolic murmurs right after surgery followed by the appearance, usually on the fourth to seventh day, of a grade 1 or 2 systolic murmur at the apex. In some instances this murmur has subsequently disappeared. While the significance of this murmur is unclear, it is presumed to represent mitral regurgitation. Such murmurs have been present in patients with normal cardiac catheterization data including normal pulmonary capillary pressures. Certainly the presence of such murmurs has not prevented the rehabilitation of the patient. Even if a satisfactory prosthetic valve were available, it would seem logical to continue utilizing annuloplasty where indicated because of its simplicity.

We must accept the fact that no patient will be cured of rheumatic heart disease. Posteromedial annuloplasty is directed to the correction of only one facet of the disease, namely, mitral regurgitation, in the same fashion that mitral commissurotomy is aimed at mitral stenosis. Frequently, more than one valve is involved as well as the myocardium. Furthermore, such patients are being operated on who are in age groups in which rheumatic heart disease is complicated by arteriosclerotic heart disease. While the surgeon attempts and hopes for a complete correction of the hemodynamic lesion, he cannot cure the disease in the usual sense and thus his goal should be rehabilitation.

Some of the early problems encountered no longer appear to be of great importance. Since we adopted the use of CO_2 layered into the operative field (8 to 10 L./minute), there has been no serious problem with gaseous embolism. Retrograde aortography has been invaluable in differentiating between aortic and pulmonary insufficiency, quantitating grossly the degree of aortic insufficiency when present and discovering occasionally a patient with serious coronary artery disease. It is recommended for all patients being considered for open mitral surgery.

SUMMARY

The open correction of mitral valvular disease, mainly in patients with regurgitation, has been carried out in thirty-three patients. Originally, it was believed that recurrent mitral stenosis and one or more episodes of systemic embolization constituted firm indications for the open operation. At present, these are not considered adequate indications. The open approach is offered only to patients with subvalvular stenosis, which has been well docu-

mented at a previous operation, who might not respond with optimum results to transventricular dilatation and commissurotomy. All repeat operations for mitral stenosis are performed now by the closed transventricular route.

In selecting patients for the open correction of predominant mitral regurgitation, with or without stenosis, the situation is more complex. If one rejects surgery for patients with associated aortic insufficiency as well as for those with mixed mitral stenosis and insufficiency and x-ray evidence of valvular calcification, the remaining patients with predominant mitral regurgitation will constitute a select group in which posteromedial annuloplasty is applicable with a low risk. Furthermore, patients re-evaluated four to forty months after posteromedial annuloplasty have, in the main, been significantly improved both subjectively and objectively.

Other methods improvised at the operating table for calcific valves with mixed hemodynamic lesions were unsatisfactory. It would appear that any procedure other than total prosthetic valvular substitution has little to offer this numerically important group of patients.

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DISCUSSION

Benson B. Roe (San Francisco, Calif.): Dr. Merendino and his group have contributed importantly to the progress in this challenging problem of reconstructive surgery of the cardiac valves. He certainly is to be commended on his results, which were presented, as usual, concisely and without excessive enthusiasm.

While our own approach to this disease has been largely toward buttressing the mural leaflet to provide better apposition of the aortic leaflet, I am willing to concede (based on the satisfactory results that were presented herein), that the simplicity and apparent durability of this posteromedial annuloplasty probably has great merit: either to replace or to supplement the buttressing of the valve, since we nearly always find some residual regurgitation at the posterior commissure.

Dr. Merendino properly has placed emphasis on the versatility necessary in the surgical approach to mitral insufficiency, since many of these valves defy any totally satisfactory repair, and until we have a well proven prosthetic replacement I am sure that many can never be returned to normal function. Those valves that have extensive calcium invasion, will never be satisfactorily improved by any plastic maneuver.

It is important to remember that many diseased valves with calcium invasion, contraction or tissue deficit can be clinically improved with a very small hemodynamic improvement because of the rather critical end point of symptom appearance on the function curve. Thus, patients whose systolic murmurs have not been obliterated may still be symptomatically better after such a procedure as Dr. Merendino describes.

Despite our own great enthusiasm from recent progress with intracardiac prosthetics and various

reported cases of temporary success, I am still convinced that we have a long way to go before valve replacement can be accepted with impunity in the routine cases.

Dr. Merendino perhaps will find greater ease, speed and perhaps even safety with the use of the left-sided approach to which we have recently shifted since this permits closer access to the valve. His drawings which depict the valve appearing through the right-sided approach show how deep it was, but in my experience the longest instruments can barely reach the valve annulus with a greatly dilated left atrium.

Through the left-sided approach the valve lies almost immediately inside the atriotomy incision, and it is easy to see it function. Furthermore, you can put a finger through the left atrial appendage to feel the results of your closure and perhaps sometimes to go back in for further repair.

Furthermore it is useful to keep in mind that closed commissurotomy through the usual posterolateral approach from the left can be converted into an open procedure in those rare and unhappy instances in which a tear is made and regurgitation is produced, or in which regurgitation is discovered at the time of the commissurotomy.

I would agree completely with Dr. Merendino that the direct vision approach for mitral stenosis leaves a great deal to be desired. We, too, are often uncertain and sometimes unhappy about the results of direct vision incision into the supposed area of commissure, and that the instruments (Dr. Gerbode's dilator and Dr. Logan's dilator) are extremely effective in producing a satisfactory commissurotomy in most instances.

Now that methods are being developed for rapid conversion of citrated blood for priming the pump oxygenator, it is reasonable to expect that a closed procedure can be converted into open cardiotomy through the same approach with minimum delay.

As Dr. Merendino has implied in his figures and the distribution of his patients that an important factor in determining the success of this operation is the selection of patients to exclude those who will provide excessive technical difficulties and those with severely diseased myocardium which will probably not withstand the procedure. The exclusion of this latter group of patients is difficult, because obviously those who are offered to us for operation are usually in severe failure, but those with intractable right-sided failure in whom the liver will not recede and the venous pressure remains high, appear to have a particularly high mortality even when a satisfactory technical result is accomplished on the valve itself.

We, too, find it impossible to predict reliably the presence or absence of intra-atrial clots. We find them when we do not expect them and we do not find them when we do expect them. Therefore, one should always be prepared to arrest the circulation to prevent massive embolization. When clots are discovered arrest must be induced instantaneously because obviously only one beat with a dislodged clot can send it to the head. We recommend the routine presence of a 4 to 6 volt fibrillating current at the operating table with sterile electrodes connected before making the atriotomy incision. A switch is immediately turned on as soon as the clot is felt and the heart is fibrillated in order to permit extraction of the clot before proceeding with the corrective maneuver.

I think that with accumulated experience these satisfactory results such as have been reported herein will expand the opportunity for corrective surgery on the mitral valve, and that we will have something to offer to this increasingly large group of patients.

Ross Robertson (Vancouver, B. C.): It appears that Dr. Merendino has changed his mind regarding the treatment of recurrent stenosis following mitral commissurotomy. He now prefers the closed operation with a dilator to open heart surgery for this condition. With this I agree heartily.

We have had thirty cases of open heart operation for mitral valve disease in Vancouver. There have been six deaths from air embolism and aortic regurgitation. I was impressed with Dr. Merendino's diagram showing the tremendous flow of blood that assails the surgeon as soon as he opens the left atrium in the presence of aortic regurgitation. It recalled some grim experiences. The aortic valve may not have much regurgitation clinically, but as soon as the pump is started and the left atrium opened there is a continuous flow backward through the aortic valve, taxing the capacity of the cardiac suction and sometimes in such a large volume that there is little blood left to perfuse the patient. This situation may be avoided by arresting the heart, as shown in Dr. Gerbode's film. For a long time we hesitated to arrest the old rheumatic heart, but in recent months we have had the courage to do this. The aorta is cross clamped and the heart perfused with cold blood until it stops. Then there is no trouble with blood regurgitating through the aortic valve. The heart is completely quiet and you can work on the mitral valve without fear of air embolism. We have had no difficulty in resuscitating these hearts, provided the left ventricle is vented so that it is not distended during the resuscitation period.

In identifying the annulus, we have found it helpful to insert a curved probe under the valve cusp, lifting the annulus so that a suture can be easily and accurately passed around it.

J. Englebert Dunphy (Portland, Ore.): I would like to congratulate Dr. Merendino on his pioneering work in this field. He is paving the way for advances along many lines.

Briefly, I would like to tell you of the work of Dr. Albert Starr at the University of Oregon with reference to the patients with mixed stenosis and insufficiency and excessive calcification. He has been using for about nine months a total prosthetic replacement consisting of a ball valve not greatly different in principle from the Hufnagel valve. Without describing the details of the valve, I will simply say that after an extensive experience in the laboratory he has gone ahead with total replacement. To date, eight patients have been operated on; there were two deaths. One of these was a technical error associated with air embolism and clearly avoidable; the other death was related to renal insufficiency in the postoperative period.

The operation is simpler than leaflet advancement although not as simple as Dr. Merendino's procedure; however, this valve replacement is being utilized in situations in which the more simple procedures can not be used.

To date, the results in the six survivors are remarkably good. The big question is, how long will a fixed valve of this type remain in the annulus and continue to function? The only thing that we can say is that in dogs it appears to be functioning well and thus far in the patients who have survived the immediate operation the results are most encouraging.

On the basis of Dr. Merendino's experiments with mixed mitral lesions one must seriously consider total prosthetic replacement particularly of the badly deformed calcific valve.

K. Alvin Merendino (closing): We have not utilized the left approach. I think it does have merit. We shall certainly explore this possibility in the future on Dr. Roe's suggestion.

Concerning the problem of clots in the left atrium, I think it is of interest that in our series we have never encountered a clot in the left atrium in a patient with regurgitation. The only clots we have seen have been in patients with mitral stenosis. I think, however, induced ventricular fibrillation with which Dr. Roe has had experience has real merit when one anticipates clots, such as in patients with ventricular aneurysms, aside from its possible value in the patient with mitral stenosis.

Concerning the calcific valves with mixed lesions of stenosis and regurgitation, there is always more valvular calcification than one sees on the x-ray film. Total replacement is the only answer for most of these patients' problems. However, I do believe that even if a total valve replacement of a prosthetic nature were available, posteromedial annuloplasty would still be of importance because of its simplicity and the ease with which it can be performed on the patients with the normal sort of valves which seem to best benefit from it.

I would like to make one more comment concerning mitral stenosis. We advise the open approach for the mitral stenosis only when there has been evidence of subvalvular stenosis, which has been well documented during a previous operative procedure, and transventricular or transatrial dilatation would not be expected to have much merit. Certainly if we had a proven satisfactory total valvular replacement, we would explore more patients with calcific mitral stenosis with consideration of replacement.

Concerning Dr. Robertson's concern about air embolism, we no longer consider this a serious problem since we have adopted the procedure of layering the field with carbon dioxide, which is heavier than air and, of course, sinks down and occupies the chambers. It is readily diffusable and does not embolize as a mass. This is usually layered into the operative field at the rate of 8 to 10 L. per minute.

Concerning cardiac arrest, we still believe it is extremely important in posteromedial annuloplasty to allow the heart to continue beating, otherwise we do not know how many sutures to use in the annulus to correct the regurgitation and we continue to use them until the regurgitation is as completely corrected as possible without producing stenosis. Therefore, the beating heart is invaluable to us.

We manage aortic insufficiency a little bit better than we used to, but our method is by clamp and generalized hypothermia down to 30°F. only. It took us an awfully long time to realize that one could not occlude the aorta completely with a tourniquet. The mass of tissue in the aorta is such that it is almost impossible to totally occlude it. If one pulls the tourniquet hard enough to occlude it, the danger of aortic transection is real.

Concerning the importance of the annulus, if you do not use sutures in the annulus you may as well stay home. There is nothing else in this area that has any strength. Therefore, Dr. Robertson's point about identification of the annulus is of extreme importance.

Again, with regard to Dr. Dunphy's comments concerning the pioneering work of Dr. Starr, I think this is a particularly exciting development. I have had the opportunity of visiting Dr. Starr and observing him put in one of his prosthetic valves. I certainly hope that his valve provides the answer to the problem, because there is a large group of patients for whom there is no hope other than with a total prosthetic replacement.

The Role of Pacemakers in the Management of Surgically Induced Complete Heart Block

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THE development of technics for cardiopulmonary bypass in the last decade has led to a new era in the management of patients with cardiovascular disease. Excellent progress has been made in the correction of many congenital cardiac anomalies which were considered incurable before the interior of the living heart became accessible to the surgeon.

One of the more serious complications associated with the closure of ventricular septal defects and atrioventricular cushion defects has been complete heart block. In patients in whom arrhythmia has occurred, complete heart block has appeared at the time of repair in virtually all instances. Fortunately, the delayed onset of complete atrioventricular block following closure of septal defects has been uncommon. The incidence of complete heart block occurring during the closure of ventricular septal defects and persisting to the end of the operation has ranged from 5 to 15 per cent, and is reportedly higher when operative correction of atrioventricular cushion defects is performed [1]. In the opinion of some authors the incidence of complete heart block increased with the widespread use of elective cardiac arrest induced by potassium citrate [2].

When intracardiac surgery was in its infancy, mortality from this complication was alarmingly high [3]. Through the judicious use of isoproterenol hydrochloride (Isuprel®)* a significant reduction in mortality was achieved, although for many months it remained at about 50 per cent. It was not until the development of the combined use of a myocardial electrode and an electrical pacemaker that mortality was reduced to a reasonably low figure [3,4]. Since that time many refinements have been made in the electronic instruments used to treat these patients. A better understanding of the anatomic location of the conduction tissue and the avoidance of myocardial ischemia have helped to reduce the incidence of the arrhythmia significantly. At the present time it occurs in approximately 5 per cent of patients undergoing repair of septal defects.

The present report will describe the clinical management of complete heart block following intracardiac corrective procedures, during both the acute phase and the convalescent period after the operation.

ETIOLOGIC CONSIDERATIONS

Little doubt exists today that mechanical interruption of the conduction system by ligation or incision results in complete heart block [3,5,6].

Experimentally, injection of certain chemicals at the base of the interatrial septum in the region of the bundle of His will produce the arrhythmia [7].

The specialized tissue of the Purkinje system like the myocardium is very sensitive to anoxia and ischemia, and complete heart block has been observed many times during cardiopulmonary bypass when the coronary circulation has been interrupted by cross clamping the aorta distal to the coronary ostia. As the period of myocardial ischemia increases, the electrocardiographic tracing progresses from that of first degree heart block to complete or total heart block and eventually ventricular fibrillation. Some authors maintain that the injection of potassium citrate into the coronary circulation for purposes of elective cardiac

* Isuprel is manufactured by Winthrop Laboratories, New York, New York.

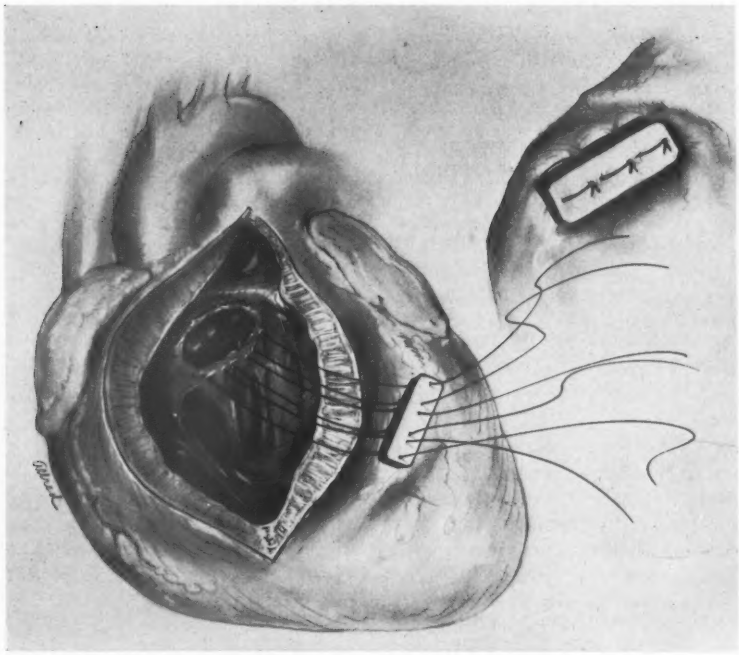

FIG. 1. Technic of closing small to medium sized ventricular septal defects. Note that the inferior margin is apposed to the superior margin. The compressed Ivalon® pledget distributes the stress of the sutures over a wide area of the muscular septum.

arrest could be incriminated as a cause of complete atrioventricular block. After elective cardiac arrest is induced in the experimental animal by the continuous perfusion of a potassium citrate-oxygenated blood solution into the coronary circulation, one will observe that when the heart is restarted a sinus rhythm returns promptly. This is in contrast to the heart whose beat has been arrested with a single injection of potassium citrate and is then restarted. In the latter, various degrees of heart block have been observed during the recovery period; this is also true following total cardiac ischemia when the root of the aorta is simply cross clamped while the heart continues to beat. These observations seem to point to the ischemic factor as being the important one in the production of the arrhythmia. The technic of hypothermic arrest during extracorporeal circulation is most commonly used today, and we know that as the temperature of the heart is decreased, atrioventricular conduction is prolonged until complete heart block often occurs. Atrioventricular conduction increases as the heart is rewarmed and a sinus rhythm resumes at 29 to 30°C.

PREVENTION

A discussion of the management of surgically induced complete heart block would not be complete without a statement concerning the prevention of the arrhythmia. Certainly prevention is the logical and ultimate goal. A number of factors in this regard should be emphasized.

Lev et al. [8] recently presented the results of extensive study of the anatomy of the conduction tissue in congenital heart disease. Surgeons supplied with this knowledge have been able to reduce significantly the incidence of complete atrioventricular block associated with the closure of ostium primum and ventricular septal defects. When possible, ventricular septal defects should be closed by approximating the inferior margin to the superior margin. (Fig. 1.) This method has been used in twenty patients and complete heart block has not occurred.

The method is suitable for closure of ventricular septal defects measuring 1.5 to 2 cm. in diameter. Larger defects must be closed sometimes by the insertion of a plastic patch which is held in position by sutures placed around the periphery. The sutures should be placed in such a manner that those located in the inferior and posterior wall do not pass through the entire thickness of the muscular septum and should be parallel to the edge of the defect. If any form of arrest is used, the heart should be restarted before any of the sutures are tied; in the event that complete heart block occurs the surgeon can identify the offending suture and remove it. If at all possible, the sutures should be placed and tied while the heart is beating; it is only by this method that one can be absolutely sure of identifying a suture injurious to the conduction system. If hypothermic arrest has been used the heart should be rewarmed and defibrillated if necessary before the sutures used to close the defect are tied. The observant surgeon, through experience and constant alertness, can avoid this complication in the vast majority of cases.

OPERATIVE MANAGEMENT OF THE PATIENT WITH COMPLETE HEART BLOCK

When complete heart block is observed after the repair of a ventricular septal defect, it is our practice to have the anesthetist administer 1 cc. of a 1:50,000 solution of isoproterenol hydrochloride (0.02 mg.) intravenously. In most but not all patients there will be an increase in heart rate and a favorable response in systemic blood pressure. This response varies unpredictably from one case to the next, and may be dependent upon the degree of metabolic acidosis present following total body perfusion. If one elects to treat the patient with isoproterenol hydrochloride the dose should be repeated at least every ten minutes in order to maintain an adequate cardiac output and a blood pressure of 90 mm. Hg systolic, or more. A myocardial electrode is then inserted subepicardially in the parietal wall of the right ventricle. We have continued to use a stigmatic unipolar electrode in the majority of cases simply because the arrhythmia is usually temporary. If a suitable bipolar electrode is available that can be removed in the postoperative phase by traction in the event that a sinus rhythm returns, its use would be preferable. In the event that complete heart block is permanent, long term stimulation can be continued with a bipolar electrode, without the danger of losing control of the heart beat.

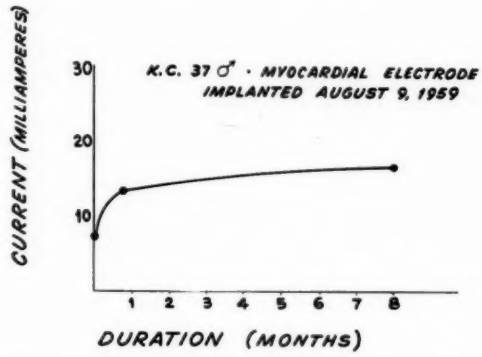

FIG. 2. The current necessary to stimulate the ventricles of a patient with complete heart block using a bipolar electrode. After the first three weeks of stimulation a plateau is reached. It has not been necessary to increase the power in over twelve months.

We have found that when a bipolar electrode is used, the current requirements to stimulate the heart increase for about three weeks after stimulation has been initiated. Then the requirements reach a plateau, and little if any increase in power is necessary after this period. (Fig. 2.)

The electrode is anchored by two fine silk sutures at the points of entrance and emergence. A loop of the insulated portion of the electrode is left inside the chest. The wire is then directed through a small stab wound in the chest wall at a point which is in line with the long axis of the buried uninsulated portion of the electrode in the myocardium. The latter is an important point to consider, for if the cable is directed away from the myocardial segment at right angles, there exists the danger of avulsing a piece of the ventricular myocardium when the electrode is removed by traction. (This complication has never occurred in our experience.) (Fig. 3.)

The segment of the electrode which emerges from the chest wall is then anchored to the skin by a fine silk suture. If a unipolar electrode is used the indifferent (positive) electrode is inserted in the subcutaneous tissue of the chest wall.

It has been our practice to connect the electrodes to the pacemaker with a sterile cable

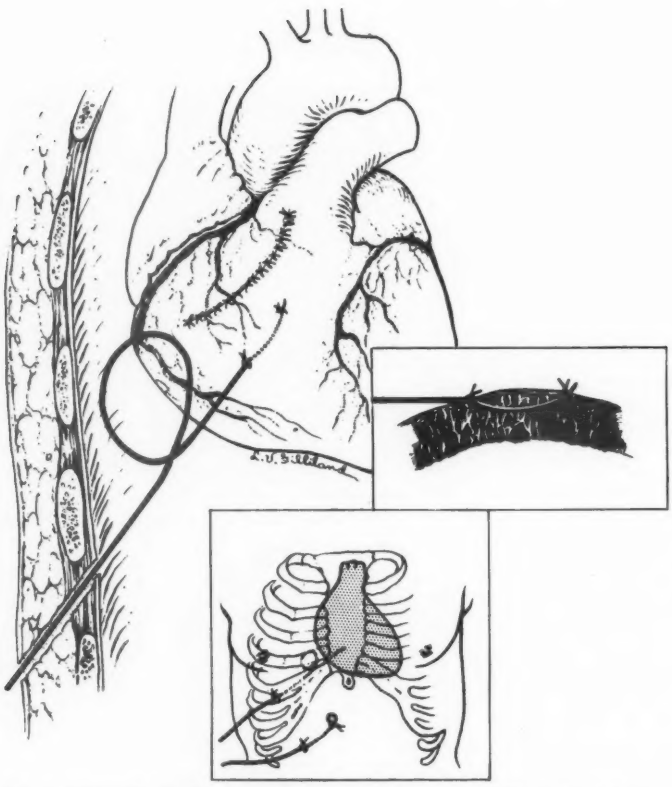

FIG. 3. The technic of implanting a myocardial electrode. The axis of the segment of the cable brought through the chest wall is the same as the uninsulated part implanted in the myocardium.

immediately and to control the heart beat elcetrically for the remainder of the operation. In children the rate is set for 100 to 120 beats per minute, and the pacemaker is turned on with the power output dial at zero. The power output dial is turned in a clockwise direction until the electrical and physical control of the ventricles is obtained. This is readily apparent to both the operating team and to the person monitoring the electrocardiograph.

In certain cases the pacemaker control of the heart will actually be lifesaving, since some patients have such a severe bradycardia and a very low cardiac output that they may die acutely unless the heart rate is increased. With battery-powered transistorized pacemakers, transportation of the patient from the operating room to the ward is no longer a problem.

MANAGEMENT OF THE PATIENT IN THE IMMEDIATE POSTOPERATIVE PERIOD

When the patient has been returned to the postanesthetic recovery room, the pacemaker should be attached to the head of the bed so that it is readily visible to anyone taking care of the patient, and an electrocardiogram taken during which time the pacemaker is turned off for a few seconds to observe the idioventricular rate. In previous publications it has been pointed out that the ventricles of the blocked heart readily give up their autonomy to the pacemaker, and the pulse will follow the flashing indicator of the pacemaker without deviation when the current is applied at threshold levels [*4,6*]. One can be confident that as long as complete heart block exists and the electrical circuit is intact, the pacemaker will

control the ventricular contractions. This fact in itself will help to determine the return of a sinus rhythm in the postoperative period, for as long as the heart rate follows the pacemaker, one can be certain that complete heart block is still present. If a sinus rhythm resumes while the patient's heart is being stimulated by the electrical pacemaker, the conversion will be apparent because the heart and pulse rate become irregular. If the heart is auscultated a rhythm is heard that appears to be due to ventricular extrasystoles and which in fact is produced by the pacemaker. The clinical impression can be verified by an electrocardiogram; the pacemaker is turned off but is not disconnected from the patient for at least forty-eight hours. Complete atrioventricular block may recur; fortunately this is uncommon, but those in attendance must be aware of the possibility. After return of a sinus rhythm the patient's pulse is monitored every fifteen minutes for six hours, then thirty minutes for another six hours, and finally, every hour for twelve hours. An order is written and the nurses in attendance are told that if the patient's pulse falls below eighty beats per minute in children and sixty in adults within the first forty-eight hours after conversion, the pacemaker is turned on and *then* a physician is called. All the nurses in our Intensive Care Unit have been taught the principles of managing these patients.

While the power output of a pacemaker connected to a myocardial electrode will vary from patient to patient, it has been found that the voltage necessary to stimulate the heart ranges from 0.5 to 3.5 volts [3,4]. It is important to mention the fact that none of these patients have ever experienced the slightest discomfort from this technic of myocardial stimulation. No difficulties have been encountered when the fine myocardial wire electrode is removed. The value of this type of therapy is greatest during the first twenty-four to ninety-six hours following operation, since this seems to be the most critical and hazardous period from a standpoint of asystole. However, a serious clinical problem exists when complete atrioventricular block persists and this will be discussed herein.

LATE POSTOPERATIVE MANAGEMENT OF THE PATIENT WITH COMPLETE HEART BLOCK

If complete atrioventricular block persists after seven days and the patient's convalescence has been satisfactory, it has been our practice to turn the pacemaker off. At this time the patient is usually given small doses of isoproterenol hydrochloride administered sublingually or rectally.

The dosage is adjusted so that the pulse rate will be maintained at eighty to ninety beats per minute. It is our belief that the smallest dose of isoproterenol hydrochloride which will produce a satisfactory rate response should be used. Most people working with this agent have found that the patient seems to become refractory to the drug in a short time. The interval that elapses before this phenomenon becomes evident varies from several days to three weeks. It should be mentioned that in patients treated with isoproterenol hydrochloride the heart rate varies considerably from one patient to another; in some patients a heart rate of eighty to one hundred beats per minute can be maintained with ease while in others it will be difficult to maintain a rate higher than forty to fifty beats per minute.

The dosage schedule of isoproterenol hydrochloride is gradually liberalized until it is given in doses of 10 to 30 mg. every four to six hours or until the patient complains of untoward side effects, of which apprehension is the most troublesome.

Although we have not implanted a bipolar electrode at the time of operation in any patient under twenty-one years of age in whom complete heart block developed at the time of repair of a septal defect, a significant late mortality has occurred in this group of patients. Two of three patients who were discharged from the hospital with persistent complete heart block have died of cardiac arrest. Despite the anticipated problems of managing children with a pacemaker for long periods, this may be the method of choice in patients who have complete heart block when discharged from the hospital.

It is reasonable to state that the patient with this arrhythmia can be managed quite successfully in the immediate postoperative period with direct electrical stimulation of the heart. Attention now must be focused on the patient with persistent complete heart block who must be treated after leaving the hospital following recovery from an intracardiac reparative operation. A satisfactory solution to the problem of long term management of these patients has not been obtained. Until we under-

stand the more subtle factors which are responsible for the development of the refractory condition that occurs during treatment with isoproterenol hydrochloride and other amines, progress from a medical management standpoint will be slow. Studies are in progress in our laboratories in an attempt to elucidate the determinants of the ventricular pacemaker.

SUMMARY

1. The use of a myocardial electrode and an electrical pacemaker enables control of the heart rate of patients with complete heart block which has occurred as a result of repair of a septal defect.

2. The mortality from this arrhythmia has been reduced significantly in the early postoperative period.

3. The problem of management of the patient with persistent complete heart block after discharge from the hospital is still unsettled.

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DISCUSSION

Norman E. Shumway (Palo Alto, Calif.): First of all, I would like to acknowledge our tremendous debt to Dr. Weirich and his associates for their invention of direct myocardial stimulation in 1957. Countless patients have been saved through this technic, and the almost insuperable problems of postoperative heart block have now been certainly largely solved.

One of the things I would like to say has to do with the convincing diminution in the incidence of heart block after discontinuing the use of potassium arrest. I think Dr. Weirich pointed to associated factors, besides local trauma, responsible for conduction problems; however in many instances, certainly, local trauma may be the least important of these several factors. It is difficult for me to think that surgeons are putting sutures in altogether different positions today from two or three years ago, when the incidence of heart block was so high. However, better perfusion technics and better types of elective cardiac arrest are no doubt responsible for this diminution in incidence.

Another point I would like to mention concerns the use of percutaneous placement of the stimulating electrode in the myocardium. Unfortunately we have had, on an emergency basis, some experience with this method. It actually is very handy and quite simple. You simply introduce a 16 gauge needle into a convenient ventricular chamber and place an insulated electrode with about 2 cm. of the tip deprived of this insulation through the needle into the ventricular chamber. Upon removing the needle, the electrode is attached to the pacemaker. Then, by slowly pulling the electrode back from the ventricular chamber, one can see the obedience between the pacemaker and the myocardial contraction, which denotes that proper contact has been made.

One other thing I would like to point out is the use of Lugol's solution, which some surgeons had unwittingly suggested as a technic for identifying the conduction system during the repair of cardiac defects. This unfortunately has a specific destructive effect on the conduction system and in these instances has caused heart block instead of identifying the area from which the surgeon should stay away.

The only other point I would like to mention briefly is that in my opinion the surgeon is there primarily to close the defect, not to identify the conduction system. Therefore, if his perfusion technic and his method of cardiac arrest are suitable, then certainly the important part of the feature is to cure the defect and not merely to try to stay away from this elusive conduction system.

Frank Gerbode (San Francisco, Calif.): I would like to compliment Dr. Weirich on his continuing interest in this field, for I believe there is still a challenge ahead of us in controlling patients with Stokes-Adams syndrome. Fortunately, fewer patients now have surgically induced heart block.

Our own experience in the last year and a half with permanent complete heart block fortunately

has been almost zero, as we have performed approximately 150 cases consecutively without this complication. Two patients who underwent repair of tetralogy and died in the immediate postoperative period had block, but we do not think this was the primary cause of death, and of course had they lived it may have occurred.

What Dr. Shumway said about changing our method of arresting the heart may have had more of an influence on lowering the incidence of heart block than the way we have placed the sutures. It is of interest, in following Dr. Lev's work, to notice that he almost always places most of the conducting mechanism on the left side of the heart. If one keeps this in mind some attempt, at least, can be made to place sutures only on the right ventricular side of the heart, rather than the left ventricular side, except in the upper aspect of the defect.

Some reference was made to the intercardial cushion defect repairs. We have performed twenty-two of these consecutively now with one death and without permanent heart block. I believe the only information I have been able to obtain from our experience in this respect has come from the fact that we have never placed a suture on the left side of the ventricular septum in closing the atrial defect with a patch. Care must be taken in the area near the coronary sinus and the inferior septal margin. In this region it is best to suture the patch to the insertion of the tricuspid valve.

In regard to percutaneous insertion of the electrode, Drs. Harkins and Ross had such an instance in our clinic about nineteen months ago. A patient whom we explored was found with some form of congenital block in a single ventricle. This patient, about the fourth or fifth day, without having undergone ventriculotomy, went into extremely slow bradycardia (thirty or forty beats per minute), and became unconscious. They passed a percutaneous electrode and restored a good solid beat. It was subsequently discontinued after about two or three days and the patient went home.

BENSON B. ROE (closing): I would like first to thank the discussers, and second to acknowledge and add my appreciation to the important pioneering and developmental work that Dr. Weirich has done in the field of pacemakers and the physiology of total heart block. Certainly this has contributed immensely to the survival of patients in whom block develops, and to the prevention of the immediate postoperative complications.

I should also like to answer Dr. Robertson's question from a previous paper by stating that we insert a large cannula in the outflow tract of the right ventricle through a purse-string or double purse-string suture. It is immediately accessible to the operative field with minimal inconvenience. If the heart does not fibrillate on routine cooling (which we use), then the pulmonary artery can be cross clamped for total diversion of the output on the right side.

I would like to ask Dr. Scarborough if he would permit Dr. Weirich to close in order to express his opinion about the percutaneous approach that Dr. Shumway has mentioned.

WILLIAM L. WEIRICH (closing): I would like to thank the discussers for their kind remarks.

I agree with everything that has been said. The percutaneous insertion of a myocardial electrode in an emergency situation seems to be a helpful method of treatment. I think there is one other point that should be made, which is that transient complete heart block can be handled very nicely today. It does not change the long term prognosis of the patient. However, if permanent complete heart block develops in a patient who is surgically considered a good risk, that patient's prognosis is much worse with this arrhythmia than it was before his defect was closed; despite Dr. Gerbode's great success in avoiding heart block, other people throughout the country still see it occasionally. I think we have to work toward a method of establishing a suitable technic to treat these postsurgical patients with permanent complete heart block.

Monitors and Clinical Judgment

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MANY of us have been involved in discussions of the curricula for premedical and medical students. In most of these discussions there is general agreement that "electronics" is a critical item in the modern curriculum. I suspect that some physicians are led to this belief because they are impressed with the array of electrical gear that surrounds the anesthetist, the cardiac surgeon and other physicians who use such instruments. I suspect also that those who look upon blinking, beeping and clicking machines that spew out reams of paper with hieroglyphic tracings or make unintelligible lines on an oscilloscope have some idea that these devices are providing answers to clinical problems that are not possible through the exercise of well developed clinical judgment. Finally, I suspect that some physicians, including those on the faculties of medical schools, are interested in including "electronics" in medical education because they believe that the modern physician needs to be a super electrician. This concept has about reached the stage at which lay people and attorneys (encouraged by the events of this electronic era) are inclined to believe that failure to employ machinery in the practice of medicine constitutes malpractice. I am inclined to believe that modern medicine is overwhelmed by gadgetry to the extent that physicians are permitting instruments to usurp clinical judgment.

I do not mean to decry the use of instruments in the practice of medicine. The study of "electronics" may provide the modern physician with knowledge that will be useful in the better understanding of transmission of nerve impulses, the changes in potential accompanying muscle action, the electrophysical factors associated with synaptic transmission, and the like. Certainly, there are many useful and dependable gadgets that provide reliable information about the patient. It is important, however, for the physician employing machines, either directly or indirectly, to be aware of their limitations. I propose to cite a few examples of standard instruments which are capable of adding to the total information about a patient but which are not capable, even in this age of cybernetics, of doing anything more than providing data which still have to be interpreted by the physician.

I have been involved in discussions with the medical staffs of hospitals in which a serious effort was being made to require routine monitoring, during anesthesia and operation, with an electrocardiograph. Such discussions were often prompted by the naive belief that such monitoring would at least diminish, if not entirely eliminate, cardiac arrests. It would be foolish indeed to debate the usefulness of an electrocardiogram. However, it would be foolish also to assume that such monitoring can compensate for the indolent, inattentive or inept anesthetist. It is obvious to all familiar with electrocardiography that this instrument reports only the electrical events taking place in the heart and it cannot represent functional competence of the heart. Changes in the electrocardiogram may presage deterioration of function, and to this extent the instrument may be useful as a monitor. There have been many documented instances in which essentially normal complexes appeared on the tracing in the presence of a completely nonfunctioning heart. As I will state several times during this discussion, the instrument reflects only one aspect of cardiac activity and the physician must be aware of this limitation and not assign to the instrument any occult powers. The electrocardiograph is useful in those patients in whom there is need to define more specifically changes that may be precipitated or augmented

by anesthetic or surgical manipulations. The instrument is not designed to supply the valuable information that can be secured by a finger on the pulse, regular recording of blood pressure, and an assessment of such common observations as color, perspiration, venous pressure, etc. Changes in the patient should be detected first by the anesthetist and surgeon and verified, if necessary, by the electrocardiograph. The reverse situation is associated usually with that category of anesthetists and surgeons whose contact with patients is indirect and who are brought into action only when a beeper actuated by the electrocardiographic complex signals a change in rhythm, or when the situation has deteriorated to the extent that obvious changes are indicated on the oscilloscope.

The market has been flooded with devices depending upon the R wave of the electrocardiographic complex for actuation of visual or audible signals. These units can reflect only one activity of the heart, its rate. For the modern anesthetist, who is expected to do many things besides administer anesthesia and keep in direct contact with the patient, such a device is useful. During those periods when he is pumping blood, fixing the light, wiping the surgeon's forehead, changing the table, drawing blood for more crossmatching, providing controlled or assisted ventilation, keeping a current chart, etc., it is nice to know if the heart is apparently beating. Again as with the electrocardiograph, this instrument reflects only the electrical activity of the heart and not its function; the instrument is still not a substitute for a finger on the pulse. It will not prevent cardiac arrest or even give an earlier warning of trouble. The early signs of disaster are detected better by the finger on the pulse assessing changes in quality of output. Changes in quality of output presage the ominous events associated with overdose of anesthetic drug, hypoxia and hypercarbia and blood loss. Cardiac arrest can occur with the same frequency in the presence of an electrocardiogram and similar monitors if the anesthetist refuses to use his clinical senses. As a matter of fact, these units have been known to beep along merrily with a heart in standstill.

One quite satisfactory and yet simple device which can provide a reasonable estimate of function of the heart is an esophageal stethoscope. This can be made from an ordinary urethral catheter and a piece of Penrose drain and, by connection with an earpiece, constant monitoring of heart sounds and respiration is a simple and direct process. More promising units have been and are being developed which measure functional activity. Most of these devices depend upon activation of photoelectric cells by changes in density due to blood flow in the finger. They can be used in association with blood pressure instruments with success, particularly in infants and small children. Unfortunately, most of the current devices are susceptible to artifacts of movement, and it is most alarming to all to have a visual or audible signal suddenly interrupted and be unaware of whether it represents a change in output or simply a shift in the position of the device. These are instruments with promise as monitors but, nevertheless, they remain useful only as aids to clinical judgment. Contrary to the electrocardiograph and the devices dependent upon the electrocardiographic complex, the units I have just mentioned are not susceptible to artifacts induced by the instrument known to recent immigrants from Iowa as the "western barbecue."

The electroencephalograph has been touted as a useful monitor. As with the electrocardiograph, this instrument depends upon potential changes and is therefore subject to the vagaries imposed by extraneous currents. With the exception of anesthetic agents such as ether and thiopental, there is no clearcut definition of patterns in the electroencephalograph associated with changes in depth of anesthesia until excessive depths are reached. The electroencephalograph may reflect reduction in blood flow to the brain but usually does so only when the reduction is pronounced and easily detected by other clinical signs. By the time clearly defined changes in the tracing can be seen, the patient has passed the early stages of difficulty from anesthesia or surgery. By this time, changes in pulse, blood pressure, respiration, etc. are readily observed. Pupillary changes are almost as indicative of the degree of brain function as the electroencephalograph. Significant deterioration is associated with nonreactive dilated pupils. Restoration of function compatible with that observed with the electroencephalograph is reflected in decrease in pupil size and improved reaction to light. The anesthetist cannot expect to manage anesthesia by substituting the electroencephalograph for clinical

observation of traditional signs, unless he elects to be consistently behind in detecting serious change.

More promising are the devices designed to provide information about the adequacy of respiration. These include such items as dynamic carbon dioxide analyzers, ventimeters, flow rate indicators and instruments for measurement of the pH, pCO_2 and pO_2 of blood. Unfortunately, except for the ventimeter and some of the flow rate devices, these instruments are so expensive, so cumbersome and so in need of well trained personnel for operation that they cannot be considered as ordinary monitors.

The ventimeter, however, is useful in providing direct measurement of tidal volume and indirect measurement of minute volume and to some extent of compliance. One's estimate of ventilation is often in error and monitoring is indicated, although not mandatory. The ventimeter or similar device is usually a simple bellows graduated to give a measurement of the amount of air moved with each breath. It is usually associated with a pressure gauge. The tidal volume can be calculated for each patient. With the ventimeter, delivery of this volume can be assured. Observation of the pressure required to move a certain volume will indicate changes in compliance. Volume flow by breath and by minute can be measured also by relatively simple and inexpensive meters inserted into the respiratory line. A reasonable estimate of ventilation can be made by observing the movements of the patient's chest and by observing the extent of movement of the breathing bag in the usual anesthetic appliance. As indicated earlier, however, it is surprising how often the estimate is in error, and usually the error is in the direction of underestimating the extent of ventilation. Hypoventilation introduces carbon dioxide retention and also may be so severe as to introduce hypoxia. Contrary to the stand taken on monitors of cardiac and circulatory function, I recommend the use of gadgets to measure respiratory function. Actually, the instruments recommended for respiration are not monitors but parts of the anesthetic apparatus, designed to measure parameters of function somewhat as do the meters on the gas machine measure output of the various gases. Monitors of respiratory function such as the dynamic carbon dioxide analyzer and pH, pCO_2, and pO_2 analyzers remain useful only as corroborative instruments for clinical judgment and are prohibitively expensive for routine use.

Monitor is defined as one who watches and warns. There is good reason to believe that almost all of the presently applied instruments can act in this capacity only in a limited sense. In the application of these various gadgets, one should establish their proper place in the evaluation of the patient. Are they to function as adjuvants to the more simple measures, or are they to serve as substitutes for constant personal contact with patients? As adjuvants, they can provide useful information which is sometimes of a more precise nature. In this capacity, however, they are more important as means for educating the hand, the eye and the ear. As substitutes, they are dangerous because they tend to encourage detachment of the physician from the patient. In addition, they are not designed to supply the sort of interpretive data that are so essential to the development and maintenance of good clinical judgment. Even computers are dependent upon the program fed into them.

The important monitors are the anesthetist and surgeon. They are the ones who watch and who are capable of interpreting the signs and providing warning and appropriate action. Whatever devices they may elect to employ to improve their clinical capacities should be recognized as being capable only of adding to their knowledge. The information provided by the instruments should be considered to be a portion, and most likely a small portion, of the data necessary for critical evaluation of the patient's condition. Unwarranted reliance on gadgetry can result only in restricted information, misleading information (at times), and deterioration of clinical acuity.

DISCUSSION

K. Alvin Merendino (Seattle, Wash.): This presentation by Dr. Cullen is a timely one.

Obviously, Dr. Cullen's aversion to certain gadgets which give information more easily obtained clinically and interpreted by a skilled anesthesiologist does not stem from any fear on his part that the anesthesiologist may be superseded by automaticity within the near future. If such gadgets are to be routinely substituted for the clinically skilled anesthesiologist, the surgeon and his patient will indeed be shortchanged. If on the other hand, the already skilled anesthesiologist

wishes to use the usual instruments as an auxillary means of monitoring the patient or to accumulate records of response to manuevers and drugs, this is most acceptable. Without doing disservice to anesthesiologists in general, it is not amiss to point out that in some quarters a breed of anesthesiologists exists which is neither skilled clinically nor capable of interpreting the messages of advanced monitoring instrumentation. The combination of an unskilled person depending upon monitoring instruments he does not fully comprehend is remindful of the halt leading the blind. This combination seems to me more dangerous than either one alone.

Dr. Cullen's remarks remind me of some of my own experiences with instruments. These experiences have conditioned a certain distrust in the exclusive dependence on such gadgets. As stated, few would deny the value of electrocardiography in medicine, yet I have experienced also the recording of a normal electrocardiogram, so described by a cardiologist, with the nonfunctioning heart exposed under my direct vision. The excursion of the myocardium during systole was so minute that it was obviously ineffective in propulsing blood; and in fact, no blood pressure was present. In this situation the electrocardiogram was less than useless, it was misleading.

I can vividly recall a nightmarish operation some fifteen years ago involving an extremely difficult anterior excision of the rectum for carcinoma with reconstruction by a low anastomosis in a very obese woman. Rather than bore you with all the details, I shall merely remind you of the vagaries of blood pressure measurements by cuff, and the inadequacies of cardiac auscultation in the obese; and, also the fact that positive pressure ventilation can produce some, although inadequate, circulation. It is sufficient to say that at the immediate conclusion of the operation both surgeon and anesthesiologist were uncertain as to whether the patient was alive or dead. An electrocardiogram settled the issue by producing an isoelectric tracing, and the patient was pronounced dead. Obviously, here the electrocardiogram was valuable in a gross way.

Between these extreme examples an obvious place does exist for special monitoring in special situations. Today if the latter patient were being operated upon one would find the constant monitoring of the heart by electrocardiogram as well as arterial and venous pressures by indwelling catheters useful. But please, not routine monitoring. Furthermore, under certain circumstances I believe dynamic CO_2 analyzers, polaragraphic measurements of the partial pressures of blood as well as pH, may be invaluable during certain neurosurgical operations particularly craniotomy, in some cardiac and thoracic procedures, and in prolonged operations in infants. Such instrumentation, however, should be put in its proper perspective in that it exists only as a part of the program to insure the safe conduct of the patient through surgery.

Certainly, I do not expect my anesthesiologist to be sophisticated in the interpretation of the electrocardiogram. Actually, the important leads are not always available to him in the operating room. Neither do I expect him to be an expert encephalographer, whatever that may be. I do expect him to be, however, an accomplished, skilled, clinical anesthesiologist. While the exploration of instrumentation is a logical one for expanding the horizons of the anesthesiologists, I am delighted that Dr. Cullen chose today to expose the limitations of certain types of instruments. The fallacy of depending upon electronic equipment may easily result in unnecessary and deleterious treatment of a well patient without diagnosing a sick one. His concept of the value of the skilled clinician and his ability to interpret and give significance to data "fed" in to him certainly agrees with my own thinking.

Unfortunately, medicine now appears to be passing through two new phases, one is the gainsmanship involved in the purchase for the operating room of ostentatious and expensive instruments which no one fully understands nor knows how to utilize to their fullest value. The second is related to the first and involves mathmanship. By the use of electronics and mathematics, old fields are being replowed. The findings are not new but dressed up to appear so because the tests are new, and are performed with new instruments and new patients. Such processed results sometimes seem rather synthetic, and remindful of a statement made in an essay by Clifton Fadiman in which he was comparing the virtues of cheese with the processed variety. Concerning the latter, he stated "the best I can say about it is that it is non-poisonous; the worst, that it represents the triumph of technology over conscience." In the context of this discussion, one could with effect substitute the word common sense for conscience. I personally hope these phases do not persist with us too long.

Basic Problems in the Management of Early Carcinoma of the Cervix Uteri

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THE CARE of his fellowman afflicted with cancer, according to the printed word, has always held the deep interest of the physician. Though we are aware that "many of the affections of the neck of the uterus were not of malignant origin" [1], it behooves the student of medical history to be ever mindful that cancer, in its present concept, is a relatively recent entity. The deep insight of the physicians of the past into the clinical manifestations of this disease more than counterbalances the occasional error in correct diagnosis. Their main interest was in the alleviation of the pain and distress usually coexisting with "cancer" and their efforts reflected the ever changing ideas, ideals and practices in the art of medicine. However, in the past as in the present, and with the same complete disregard for the welfare of the afflicted, the most preposterous claims were made by the inept, the inexperienced and the untrained.

It is not the intent of this report to propound a new theory of origin or cause, nor to propose a new system of management, rather it is to emphasize some of the shortcomings in our present methods of treatment. In reviewing the literature from 1945 to the present, it is discouraging to note the number of articles acclaiming the value of so-called radical surgery and the paucity of comments on its attendant pitfalls, dangers and inadequacies.

MATERIAL

The complete records, the surgical procedures and the surgically excised tissue of eighty-three patients, who were pre- and postoperatively classified by the surgeon as having carcinoma of the cervix uteri in clinical stage 1, have been reviewed. In each case the pre- and postoperative surgical procedure was listed as a "radical hysterectomy and bilateral lymphadenectomy." This series represents the surgical effort of thirty-six physicians working in eleven different hospitals, and patients who were followed for a maximum of twelve years and a minimum of two and one half years. This is not a consecutive series, as over one half of the originally collected cases were discarded because of inadequate records and/or follow-up. It is unfortunate that we do not have a similar series of patients who were treated with radiotherapy.

In each case the size and gross appearance of the primary lesion were based on the records of the examining physician and the pathologist. The length of the vaginal cuff and the extent of the lateral excision were obtained from the pathologist's description of the surgical specimen prior to blocking and fixation. The blatant loopholes inherent in data so obtained are apparent and the statistics relative to these points are included (Table 1) as estimates rather than factual findings.

The gross and microscopic data were reviewed, and in approximately 50 per cent of the cases additional microscopic examinations were made. Unfortunately for statistical accuracy, necropsy studies were available for only twenty-seven of the fifty-one deaths; thus, the exact cause of death in twenty-four of the cases was based on clinical deductions. Neither the incidence nor the importance of unrecognized but possible active malignant processes are known for those patients who died of causes not attributed to the primary cancer. However, in this relatively small series, we are certain that those cases listed as "cancer deaths" were typical enough to permit this interpretation even in the absence of necropsy.

TABLE I

COMPILATION OF EIGHTY-THREE SURGICAL SPECIMENS, RECORDED AS RADICAL HYSTERECTOMY AND BILATERAL LYMPHADENECTOMY FOR THE TREATMENT OF CERVICAL CARCINOMA, PREOPERATIVELY CLASSIFIED AS CLINICAL STAGE I

Group and Estimated Size of Primary Lesion	Total No. of Patients	Postoperative Clinical Stage		Length of Vaginal Cuff		Nodes Removed		Positive Nodes	Tissue Extension	No. of Patients Who Received Postoperative Irradiation	Total No. of Deaths (12 yr.)	Deaths from Primary Lesion	
		No. of Patients (error)	Stage	No. of Patients	Inches	No. of Patients	Range No. of Nodes (average)					No.	Per cent
Group A, 1 cm. or less.....	23	(27%)	...	...	...	...	...	...	...	7	12	8*	35
		2	0	12	0	17	0	AC 11	AC 6				
		18	I	8	½	4	2–8(5)	AC 20	AC 14				
		3	II	3	¾	2	10–12(11)†	...	...				
Group B, 1 to 2 cm.....	31	(19%)	...	...	...	...	...	...	...	8	17	13‡	42
		1	0	7	0	8	0	BC 3	BC 7				
		25	I	16	½	7	2–5(4)	BC 7	BC 23				
		4	II	8	I	10	6–9(7)	BC 13	BC 24				
		1	III	...	...	6	10–11(10)	BC 29	BC 29				
Group C, over 2 cm.....	15	(33%)	...	...	...	...	...	...	...	6	11	8§	53
		10	I	2	0	4	0	CC 3	CC 7				
		4	II	7	½	4	2–4(3)	CC 7	CC 8				
		1	III	6	I	7	5–10(7)	CC 15	CC 15				
Group D, size not estimated (cervix cauterized before surgery)	14	(43%)	...	...	...	...	...	...	...	6	11	9	64
		8	I	6	0	0	0	0	DC 4				
		4	II	5	½	0	0‖	0	DC 7				
		2	III	3	I	0	0‖	0	DC 10				
		.....	...	...	...	...	...	...	DC 14				

* One patient reclassified as stage 0 died of surgical complications; this case is not listed as a cancer death.

† Only one had eleven nodes.

‡ The one surgical death is not reported as a cancer death.

§ The six patients who received irradiation therapy are included.

‖ Although no nodes were found after careful examination, extension into the paravaginal tissue was noted in the four patients described in the text (see dispersal).

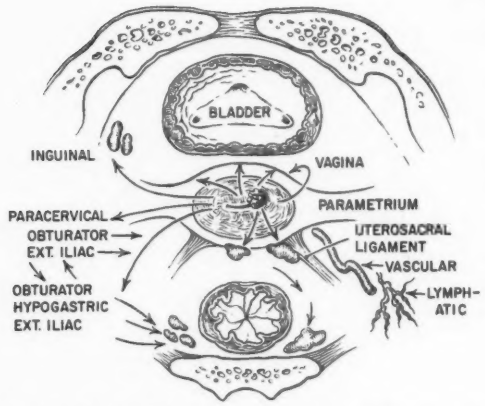

FIG. 1. The spread of cervical cancer by hematic and lymphatic routes and by continuity and contiguity.

THE NATURAL HISTORY OF CERVICAL CARCINOMA

Contrary to the occasional report, it is our belief that the invasive stage of cervical carcinoma is invariably preceded by localized cellular changes interpreted as noninvasive carcinoma, carcinoma *in situ* or intraepithelial carcinoma. This localized process is readily diagnosed and, if correctly evaluated and properly managed, completely curable. However, with the first break-through or evidence of invasion as disclosed by microscopic examination of the excised cone, both the lesion and its host acquires a new and potentially lethal status. Unfortunately, neither the size nor the cellular grade of the primary lesion, the age or parity of the host nor the duration of the signs and symptoms predicate the presence or absence of the spread of cancer. Though the implications of the terms *early* or *small*, as applied to cervical cancer, are fully appreciated by most they are basically misleading as they imply limitation of the disease to the cervix and, therefore, is curable.

Despite the tremendous advances in the field of science, we are still unable to predict either the growth rate of the tumor or the direction and rapidity of spread. Possible factors responsible for these unpredictable variables include the following: the cellular index; the physiologic and/or psychologic status of the host; and the interesting and probable, important but still imponderable, "biologic factors," "host resistance," et cetera. However, it is evident that neither experience nor equipment permit an unequivocally correct estimate of the clinical extent of the disease without the meticulous examination of excised tissue.

The presence of spread (Fig. 1), be it by continuity, contiguity or by the vascular or lymphatic channels is difficult to demonstrate, especially in the early stage of the disease. It is our contention that careful examination of all potential metastatic sites reveals malignant spread beyond the confines of the cervix in at least 20 per cent of those patients, classified before and during surgery, in clinical stage I. The reported variations in the percentage of positive lymph nodes in this group at the time of surgery are readily explained on the basis of (1) the amount of node-bearing tissue excised, (2) the extent of the lateral and circumcervical excision and (3) the thoroughness of the pathologic examination. The fairly constant error in the clinical estimate has been emphasized previously [2,3] but, as this report reveals, it does not reflect the incidence of error prevalent in material gathered at random.

OBSERVATIONS

To list all of the observations would be both cumbersome and confusing. We are, therefore, including only that data essential to this report and for added clarity dividing the series into four groups. (Table I.) In each case, the pre- and postoperative records listed the surgical procedure as a radical hysterectomy and bilateral lymphadenectomy. Stage 0 is used throughout instead of the admittedly better but more unwieldy term of intraepithelial carcinoma. The dispersal of patients with cancer spread beyond the confines of the cervix is as follows:

Group A
- CASE I. (AC6) 33 years; para V; posterior spread in ½ inch cuff; no nodes removed
- CASE II. (AC11) 48 years; para III; one positive node in 3; no cuff
- CASE III. (AC14) 37 years; para V plus; anterior spread in ¾ inch cuff; no nodes
- CASE IV. (AC20) 49 years; para VI; one node in 6; ½ inch cuff

Group B
- CASE I. (BC_3) 30 years; para II; 2 of 6 nodes positive; no vaginal cuff
- CASE II. (BC7) 44 years; para IV; 1 of 8 nodes positive; anterior spread in one inch of cuff
- CASE III. (BC13) 37 years; para VII; 2 of 5 nodes positive; ½ inch cuff

Case IV. (BC23) 62 years; para II; anterior spread in ½ inch cuff
Case V. (BC24) 34 years; para I; posterior spread in ½ inch cuff; no nodes
Case VI. (BC29) 39 years; para IV; 3 of 8 nodes positive; anterior and posterior spread in one inch cuff

Group C

Case I. (CC3) 39 years; para V; 2 of 6 nodes were positive; no cuff
Case II. (CC7) 37 years; para III; 1 of 3 nodes positive; anterior and posterior spread in 1 inch cuff
Case III. (CC8) 48 years; para VI; no nodes removed; posterior spread in ½ inch cuff
Case IV. (CC15) 43 years; para II; 5 of 9 nodes positive; anterior and posterior spread in 1 inch cuff

Group D

Case I. (DC4) 61 years; para IV; anterior spread in ½ inch cuff
Case II. (DC7) 33 years; para V; anterior, posterior and lateral spread in 1 inch cuff
Case III. (DC8) 41 years; para III; posterior and left lateral spread in ½ inch cuff
Case IV. (DC14) 39 years; para I; anterior spread in ½ inch cuff

Experience supported by diligent observations have made the following basic precepts mandatory for the management of the patient with carcinoma of the cervix uteri: (1) a complete preoperative evaluation of both the patient and her disease; (2) a comprehensive effort to establish an optimum physiopsychic status regardless of the planned type of treatment; (3) an intelligent, conscientious and discriminative review of the entire problem not only by the operating surgeon, but in cooperation with an internist, a radiotherapist and a pathologist; and (4) diligent and judicious postoperative care and follow-up.

With these precepts in mind, the complete records of each case were analyzed; the following are some of the noted omissions and additions: (1) the entire preoperative examination in fifty-five cases (66 per cent) was limited to routine measurement of blood pressure and pulse rate, vaginal palpation, cervical visualization and biopsy and a routine blood count and urinalysis of a voided specimen.

(2) In twenty-eight cases (33 per cent), there was routine measurement of blood pressure and pulse rate, vaginal and rectal palpation, cervical visualization and biopsy and a routine blood count and urinalysis. Additional examinations included roentgenographic examination of the chest (five cases), determination of coagulation-clotting-prothrombin time (nine cases), analysis for blood urea nitrogen (two cases), sigmoidoscopy (three cases) and complete survey of the urinary tract (two cases).

(3) We based the number and type of consultations on the written comments. The possibility of "curbstone" consultations is admitted, but we hold that if advice is not worth recording it has no value. The consultants included general surgeons in five cases, a general surgeon and radiologist in three cases and, for some unexplainable reason, an orthopedist in one case. The consultants' comments did not disclose any disagreement, nor did they include any constructive advice concerning the contemplated plan of treatment, the preoperative preparation of the patient or the postoperative management.

(4) The medical and surgical training and background of each of the thirty-six participants in this series, based on one or more hospital staff application forms, disclosed the following: seven of the thirty-six were certified by The American Board of Surgery, nine were certified by The American Board of Obstetrics and Gynecology of which five were trained primarily in obstetrics, thirteen listed themselves as general surgeons and were not considered eligible by the Board on the basis of training and experience and seven identified themselves as "general" and listed their training as one to two years of rotating internship in nonteaching hospitals.

(5) Regardless of the hemoglobin report, each of the eighty-three patients received an average of 3.2 units of blood during and/or following surgery. The records disclosed that each of twenty-three patients received 1 unit, seventeen had 2 units, fourteen had 3 units, ten had 4 units, three had 5 units, seven had 6 units, five had 7 units, one had 8 units, two had 10 units and one had 12 units. A total of 271 units of blood were employed for eighty-three patients who had, essentially, a simple total hysterectomy and a bilateral salpingo-oophorectomy. Each patient also received an average of 2.8 L. of various combinations of glucose between the start of the operation and midnight of the same day. An effort to correlate the units of blood given, with either the reported blood count or the stated estimate of blood loss during surgery, was impossible. It

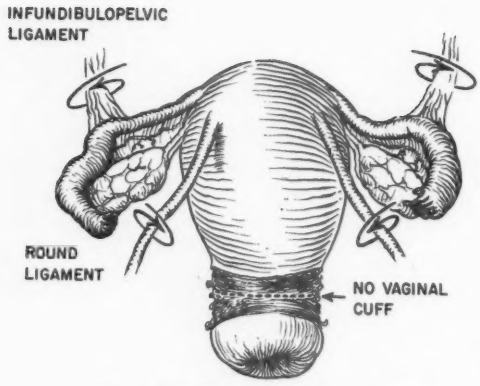

FIG. 2. Simple total hysterectomy.

was our impression that in the majority of cases both the pre- and postoperative orders suggested routine rather than careful survey of the patient and her possible needs before, during and following surgery. It was also apparent in some cases that the postoperative complications were more common in patients receiving too much rather than too little parenteral fluids.

As previously noted, to analyze and report all of the pertinent information obtained in this study would result in confusion; therefore, the material has been culled for the data essential to emphasize our contention that there is no short cut in the practice of good medicine.

When the diagnosis was cervical carcinoma in clinical stage I and extensive investigations disclosed no contraindication to the surgical approach, the operation most frequently advocated was radical hysterectomy with bilateral lymphnodectomy [4]. Unfortunately, even in the accepted specialized cancer centers a radical hysterectomy has many meanings. The reasons for this wide discrepancy, in the interpretation of a surgical technic which has been accurately described, are unexplainable. I consider a radical hysterectomy to include a generous vaginal cuff, all of the paravaginal and paracervical tissue and a wide wedge of the parametrium.

Observations, gleaned from a review of surgical records, pathologic specimens and reports and the literature, reveal that to some surgeons a bilateral lymphadenectomy is a meaningless but attractive term adding unmerited and unwarranted stature to a procedure planned but rarely consummated; to some it is the removal at random of a few fragments of retroperitoneal fatty tissue. To others, it is the careful, conscientious effort to remove as many of the lymph nodes and lymph channels as possible. Such redundant descriptive terms as complete, meticulous, *en bloc* or thorough are misleading as they imply the removal of all of the nodes, a task admittedly impossible.

The careful review of the surgeon's description of the procedure and the pathologist's analysis of the submitted specimen permit the following observations (Table 1): (1) No vaginal cuff was identifiable in twenty-seven patients (33 per cent). Actually in most of these cases it was evident that all of the cervix had not been excised. (2) Though we credited thirty-six patients (43 per cent) with at least ½ inch of cuff, in almost half of these the rim of the cuff was so narrow that it was barely recognizable. (3) In twenty patients (24 per cent), the length of the cuff varied from ½ inch to a meager 1 inch. We are cognizant of the consistent discrepancies between the linear measurements made at the time of surgery and those with similar measurements made by the examining pathologist. These differences represent the expected variations due to the release of tension or pressure, dehydration and the distortion from fixation.

Any operative procedure, planned and performed for the laudatory purpose of curing a patient of her cancer, must necessarily include the complete removal of not only the primary lesion but also all of the potential metastatic routes and sites. If the scope of excision in this series is based on the surgeon's description of what was clamped, cut and tied, an adequate radical hysterectomy was performed on each of the eighty-three patients. However, if the extent of the surgical procedure is interpreted in the cold light of the pathologist's report, approximately one half of the patients had little more than a simple total hysterectomy (Fig. 2); in the other cases, the operation could be listed as a very incomplete radical hysterectomy. (Fig. 3.)

Lymphadenectomy, like radical hysterectomy, has many meanings to many people. Again, the discrepancies in its application are difficult to explain unless one resorts to the rather uncomplimentary thought that to some probity is synonymous with perfidy. Another imponderable is why those with the least experience inevitably try to remove the lymph

nodes by the transperitoneal approach. Experience has definitely revealed that the retroperitoneal technic permits better exposure with less complications.

In reviewing the reports on tissue submitted during the performance of bilateral lymphadenectomy, the following observations were made: (1) Diligent search revealed no nodes in forty-three cases (52 per cent). (Table 1.) In thirty-one of the forty-three cases no specimen, even suggesting an attempted excision of possible node-bearing tissue by which to lend credence to the purported lymphadenectomy, was submitted. (2) In forty cases (48 per cent), the number of identified nodes varied from two to eleven; however, not a single specimen was tagged, thus thwarting any opportunity for theorizing the possible extent or direction of nodal spread.

In reviewing data obtained by autopsy [2,3], the average number of nodes removed and identified from subjects who had not received irradiation treatment varied from eighty to 100. Thus, the validity of the statement that the piecemeal removal of five to ten nodes has little value, may increase the incidence and rapidity of metastases and certainly reflects questionable surgical practice.

Postoperative Observations. In none of the cases did the postoperative management, except for a possible increase in parenteral fluids, differ from that employed with the patient who had had a total hysterectomy for benign disease of the uterus.

The surgical complications included five vesicovaginal fistulas, one severed ureter in a patient from whom 1 inch of cuff and seven nodes were removed and one surgical death. The latter was that of a twenty-seven year old unmarried woman with a stage 0 lesion. Three patients had intestinal obstruction which required surgical intervention.

The postoperative management of the patients, with or without positive nodes or tissue spread, revealed no consistent pattern. Four of those with positive nodes and two with tissue spread received varying but consistently inadequate amounts of external irradiation. Five of the patients in stage II and one in stage III received what is accepted as adequate external irradiation. The reasons behind this failure to utilize every available modality in the treatment of this disease, even in the presence or absence of extension of tissue but with the knowledge that the surgery has been inadequate, are not understood.

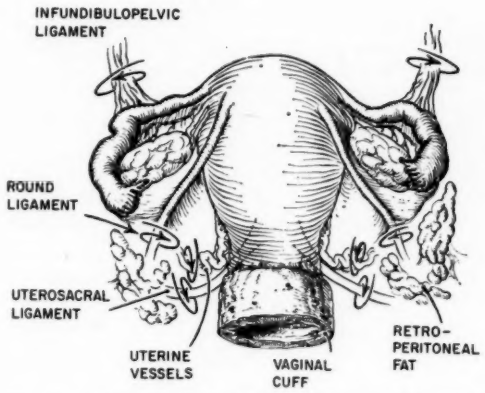

FIG. 3. Inadequate "radical hysterectomy and bilateral lymphadenectomy."

COMMENTS

In studying the anatomicophysiologic relationships of the paravaginal, paracervical, parametrium and the lymphatic channels and nodes to the cervix, it is logical to theorize that the lateral or parametrial spread would be the first and most common route. From the literature, it is evident that this hypothesis is accepted by the majority of investigators and clinicians. Though our observations tend to support this route, they also lend emphasis to the importance of spread either by continuity or contiguity. Thus, surgery undertaken with the purpose of cure must include not only the lateral tissue but also all of the tissue encircling the cervix and the upper vaginal vault. Despite improved equipment and technics, the presence of these nests of malignant cells are rarely recognized except by careful microscopic examination of the excised tissue. Simply stated, it is evident that even in the so-called early clinical stage of this disease, it is possible to have both node and tissue involvement. It is also evident that our present accepted classification of the clinical stage of this disease is, at best, an inadequate makeshift. The final estimate is made by the pathologist and not by either the radiologist or the surgeon.

The clinicopathologic data, based on some of the observations of only eighty-three cases of "early" cervical carcinoma, are not reported with any intent of entering the groundless controversy of the superiority of surgery over

irradiation or vice versa. Our ideas on treatment concur with those of Thomas [5], who in 1880 wrote, "No practice in reference to this disease can be so pernicious as that based upon the idea that because there is cancer of the uterus* some surgical procedure must be resorted to . . . if the operator be convinced that decided benefit is to accrue to the patient from surgical interference, it should be practiced; not otherwise." The same pernicious practice applies equally for those holding that irradiation is the only therapy. There is no stereotyped plan, for it is recognized that surgery even in its most radical extent and irradiation at its very best are often inadequate.

There is only one problem, the patient and her disease; and the only concern is making available to those involved the best that medical science has to offer. Regardless of the form of therapy, be it the scalpel, the ray or the cautery, the experience is deeply traumatic not only physiologically but also psychologically. An overlooked dietary inadequacy, a disregarded chronic infection or the failure to appreciate the involved psychologic aspects are important to the better management of this disease.

That the importance of the complexities involved in the management of cervical cancer is either disregarded or not appreciated is evidenced in this series by (1) the inadequate preoperative survey and preparation of the patient, (2) the inadequacy of the surgical excision and (3) the low salvage rate. The follow-up studies included two patients followed for twelve years, three patients for eleven years and seventy-eight patients for a maximum of six and a minimum of two and one-half years. Of these five patients, two were reclassified as stage 0, in extent, and are still free of the disease. Of the three classified as stage 1, in extent, two are still free of the disease and one died as a result of her primary disease seventeen months following surgery. For the seventy-eight patients followed for an average of four and two-tenth years, the salvage rate is 53 per cent. If, however, seven additional cases, interpreted as highly probable but not proven cancer deaths, are included the salvage rate plunges to a low of 44 per cent.

According to the literature, the salvage rate for the type of patients included in this series, regardless of the therapeutic modality, varies from 70 to 90 per cent. These rates reflect the effort of highly experienced teams working in well equipped hospitals under ideal conditions. It appears probable, from the observations reported herein, that too many inexperienced physicians are accepting these high salvage rates as being applicable to all patients with cervical cancer including those operated on in poorly equipped hospitals under extremely unsatisfactory conditions.

Further comment on these observations concerning the importance of the intelligent and diligent management of this disease would add little.

* Cancer of the uterus includes both cervical and fundal carcinoma.

CONCLUSIONS

1. The surgical efforts of thirty-six physicians in treating eighty-three patients with cervical carcinoma, stage 1, by radical hysterectomy and bilateral lymphadenectomy are reviewed.

2. Failure to appreciate the importance of an intelligent preoperative survey, lack of discriminative judgment in the choice of therapy and inadequately planned postoperative care are reflected in the salvage rate of 44 per cent.

3. The lack of correlation between the surgeon's description of the surgical excision and the pathologist's report stress the inaccuracy of recorded data.

4. Misconceptions of the vagaries of cancer during the so-called early stage of this disease are revealed by the inadequate excision of tissue and absence of proper postoperative management.

5. The indiscriminate and improper use of the term radical hysterectomy and bilateral lymphadenectomy is reported as employed in each of the eighty-three cases.

6. No words or phrases would impart a minute of dignity to the practice of medicine as observed in this reported series.

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DISCUSSION

Howard C. Stearns (Portland, Ore.): Cervical carcinoma is a serious and tragic disease. It is miserably lethal when not cured and often terminally associated not only with severe pain, hemorrhage and constant vaginal discharge, but also with complete loss of control of the bowel and bladder.

When confronted with the management of such a problem, the wise and conscientious physician will utilize the most modern methods of therapy or will direct the patient to someone capable of giving such care. Dr. Henriksen's paper presents an experience in surgical mismanagement of cervical carcinoma that is duplicated in virtually every community in this country even to this day. Regrettably, the story could be paralleled in the matter of irradiation therapy of the same disease in any community, and the patient is the loser.

Certain fundamental factors of this neoplasm should constantly be borne in mind by one charged with the responsibility for therapy of cervical cancer. These include modes of spread, directions of spread, extent of spread, degree of infection associated with the tumor, degree of anemia and others. The physician must wisely choose radiation therapy or surgery or possibly a combination of both modalities. Principally, he must be aware that once the program is outlined and therapy consummated, the die is cast and there is no turning back. One cannot back track and correct his errors. The therapy in each individual case should be planned and executed like a man's first parachute jump for there is not generally a second opportunity for success.

Dr. Henriksen's message does not involve the discussion of irradiation versus surgery in management of cervical carcinoma, but I think it is proper to interject it here. Each field has its advocates and each modality has its values. My early training in the radical Wertheim operation was under Dr. Raymond Watkins, a former member of this Society. I have observed and worked with many fine men who have used this procedure and I can honestly say Dr. Watkins was among the most skillful. In spite of the fact that we limited the operation to young lean patients in clinical stage I, we had an occasional postoperative death. The principal damage was to the bladder, rectum and ureter which occurred in over 10 per cent of all patients; this was usually in the form of fistulas. The five year survival rate was less than could be obtained by using radium and deep x-ray therapy, modalities which if properly used have a low injury rate to such tissues. In 1947, Dr. J. V. Meigs, a more recent advocate of the radical Wertheim operation for cervical cancer, wrote, "It should be distinctly understood and emphasized that the operation is not an attempt to compete with irradiation in cancer of the cervix. Irradiation is the present treatment of choice and it has not been proved that the surgical procedure is as good or better. Surgery should distinctly not be made the goal of all operating surgeons for all but a very few cases are much better handled by irradiation."

If such is the opinion of a well trained pelvic surgeon as Dr. Meigs, then each of us should evaluate carefully the method of management of every cervical malignancy we encounter. Dr. Henriksen's paper should be widely distributed to hospital staffs where the policing of therapeutic procedures is best carried out.

Dr. Henriksen has reported a problem that I am sure exists in every community. He did not discuss the matter of its correction. In this light, I suggest that a much better and more extensive training in gynecologic surgery during the residency of the general surgeon would be of marked value in correcting the somewhat inadequate therapy of this lesion which is so commonly practiced. Conversely, the gynecologic surgeon should be much more widely trained in general abdominal surgery and urologic surgery. In addition, the tumor committees in each hospital should administer discipline in the management of malignancy and should promote an educational program to correct the apparent occurrence of inadequate management of this serious disease.

Erle Henriksen (closing): Twenty-five years of clinical and pathologic observations strongly support my contention that the over-all management of both cervical and uterine cancer is depressingly poor.

The low salvage rates are indisputable evidence that too many inadequately trained physicians usurp their rights and privileges and completely neglect their responsibilities.

Independent Primary Malignant Neoplasms Following Mastectomy for Breast Carcinoma

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THE occurrence of multiple independent primary malignant neoplasms in the same subject is being observed with increasing frequency, owing in part to increased longevity and better diagnostic and therapeutic facilities [1–6]. Carcinoma of the breast has the highest occurrence rate of any malignant neoplasm in the female [7]. Hence, it is statistically logical that some proportion of persons who have had an apparent cure of a breast carcinoma will have another independent malignant neoplasm later.

Patients with independent primary malignant neoplasms following mastectomy for carcinoma of the breast may be divided into three groups. First, there are a few in whom independent lesions develop in both breasts simultaneously. This may be discovered at the initial examination but sometimes is not recognized until some weeks or months after one breast has been removed. Second, there are those in whom an independent primary lesion develops in the remaining breast after radical mastectomy. In the third group are those in whom an independent primary lesion develops in another organ after an apparent cure of a primary carcinoma of the breast.

Although clinical differentiation between independent primary and metastatic lesions is difficult, making this difference is obviously important because independent primary lesions of other organs or of the breast, either bilateral simultaneous or bilateral nonsimultaneous, may be curable by radical therapy. Metastatic lesions to other organs or the contralateral breast are considered to be inoperable and the prognosis relatively hopeless [8]. Never should a lesion in another organ or the remaining breast of a patient who has had a mastectomy for breast carcinoma be assumed to be metastatic. Necessary biopsy to establish the diagnosis may require craniotomy, thoracotomy or laparotomy. Occasionally an independent, potentially curable primary lesion will be found.

MATERIAL AND METHOD

The material for this report was taken from the clinical records of 355 patients with carcinoma of the breast seen at a private general hospital in San Francisco between 1947 and 1959. During this twelve year period 2,172 primary independent malignant neoplasms were observed. Carcinoma of the breast made up 16.3 per cent of all malignant lesions and 28 per cent of all malignant lesions found in females.

Each record was carefully reviewed for the development of a second independent primary malignant neoplasm. Patients in whom the first cancer was not in the breast were excluded. In each patient the diagnosis was based on unequivocal histologic evidence.

Bilateral Simultaneous Breast Carcinoma. We agree in general with the criteria proposed by Guiss [9] for the selection of patients with bilateral, simultaneous breast carcinoma: "(1) The patient must present clinically independent lesions in each breast when first seen and be free from evidence of metastatic lesions. (2) The history must be that of concomitant development of independent tumors. (3) The patient's clinical course following bilateral mastectomy must be free from evidence of early local recurrence which would suggest that the bilaterality of the process was merely metastatic in nature." We do not accept fully the requirement that independent lesions must

be found when the patient is seen initially, but would extend this up to six months, which would allow time for an occult carcinoma present in the contralateral breast at the time of the first examination and mastectomy and clinically not detectable, to become recognized.

Bilateral Nonsimultaneous Breast Carcinoma. We agree with the criteria proposed by Moertel and Soule [*10*] for the selection of patients with bilateral nonsimultaneous breast carcinoma: "(1) Each lesion must be proved to be of unequivocal malignancy by pathological examination. (2) The first lesion must have been removed by mastectomy with reasonable hope of cure at least six months prior to the diagnosis of the second lesion. (3) At the time of diagnosis of the most recent lesion, there must not be any evidence of local recurrence of the initial lesion or of distant metastasis."

Independent Primary Nonmammary Cancers Following Mastectomy. Warren and Gates [*1*] and Slaughter [*3*] have discussed the criteria by which one may select patients with multiple malignant lesions. We used the following criteria to select these patients: (1) definite evidence that mastectomy (or mastectomies) had been performed for carcinoma; (2) definite pathologic evidence of malignancy of the second tumor; (3) the absence of metastasis or recurrence of the carcinoma of the breast and of distant metastasis of the second tumor; (4) Some definite histologic difference between the two tumors. Four cases of carcinoma of the ovaries were excluded because there was evidence of widespread metastasis of the breast cancers and it could not be said for certain that the ovarian lesions were independent. There were perhaps more carcinomas of the skin in the patients in the present study than is reported here in that many patients may have had a small skin cancer removed elsewhere and the diagnosis never recorded in their clinical hospital records. For example, six cases in which there was a history of a small skin cancer reported but the diagnosis not documented pathologically were excluded from the series.

RESULTS

In the twelve year period 1947 to 1959, 355 patients were treated for cancer of the breast at the French Hospital in San Francisco. In thirty-four of them (9.9 per cent) a second independent primary malignant neoplasm developed. Seven had bilateral simultaneous breast cancers, nine had bilateral nonsimultaneous breast cancers and eighteen had independent primary nonmammary cancers. (Table 1.)

TABLE 1
OCCURRENCE OF INDEPENDENT MALIGNANT NEOPLASMS FOLLOWING MASTECTOMY FOR BREAST CARCINOMA (IN 34 OF 355 PATIENTS)

Malignant Neoplasms	Number	Per cent
Bilateral simultaneous breast cancer	7	2.0
Bilateral nonsimultaneous breast cancer	9	2.5
Independent primary nonmammary cancer	18	5.4
Total	34	9.9

In Figure 1 the results of treatment of seven patients with bilateral simultaneous breast cancer are presented. All were postmenopausal. The range in age was from fifty-seven to seventy-seven years, the average being 67.8 years. The duration of symptoms ranged from one month to four years before mastectomy. In all patients the first symptom was a painless lump in the breast. The diagnosis was made at the first examination in three instances. In the remaining four patients the second tumor was not discovered until after one breast had been removed; the size of the tumor in the contralateral breast in these patients was large enough to suggest that they may have been present at the time of the first examination. In two of these four cases the second tumor was noted by the patients; in the other two, by the physician. In five of the seven cases there was some definite histologic difference between the two tumors.

In two of these patients bilateral radical mastectomy was performed at one operation; whereas, in another, radical excision on one side and simple mastectomy on the other side was carried out at the same time. The remaining four patients had the second breast removed from two weeks to three months after the first. Three received postoperative roentgen ray therapy.

In this group of seven patients, four are alive and free of recurrent disease from fourteen months to six years after bilateral mastectomy.

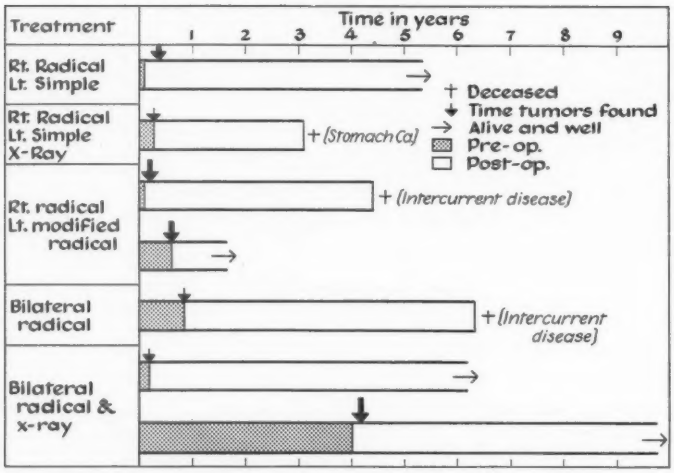

FIG. 1. Results of treatment in seven patients with bilateral simultaneous breast cancer. The four heavy arrows indicate the second breast cancer was discovered shortly after one breast had been removed. Modified radical mastectomy indicates the pectoralis minor was not taken.

Four of the patients have survived over five years. None of the three patients who are dead died of carcinoma of the breast. One died of a perforated carcinoma of the stomach twenty-eight months after bilateral mastectomy. At necropsy there was no evidence of recurrent breast cancer. She had had vague abdominal symptoms with anemia and loss of weight for six months, but the possibility of an intra-abdominal primary nonmammary malignant lesion was not considered. The other two died of intercurrent disease with no evidence of recurrent cancer of the breast at necropsy.

In Figure 2 the results of treatment of nine patients with bilateral nonsimultaneous breast cancer are presented. The age range at the time of treatment of the first breast cancer was from thirty-two to seventy years, the average being 49.9 years. The interval between the first mastectomy and the second ranged from

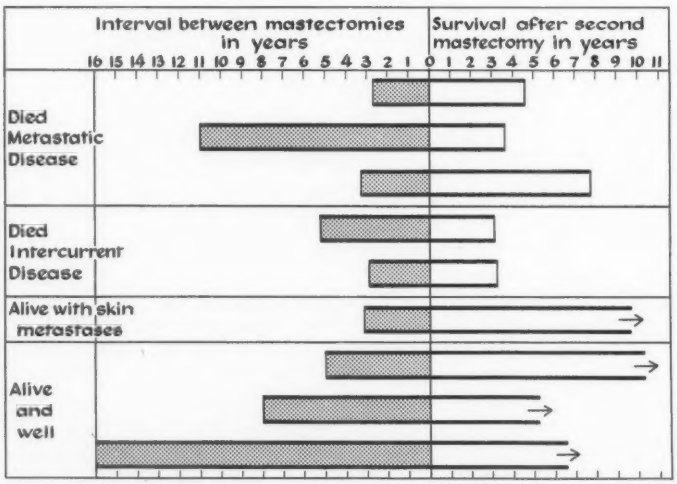

FIG. 2. Results of treatment in nine patients with bilateral nonsimultaneous breast cancer. (Cases 1 to 9 reading from top.)

thirty-two months to sixteen years. These patients all had radical mastectomy and two (cases 1 and 4, Fig. 2) received postoperative roentgen ray therapy.

Of this group, five patients are dead and four alive. Of the five who are dead, three died of cancer of the breast and two of other causes. Three patients are alive and free of recurrent disease after sixty-three months to over ten years following the second mastectomy. One patient is alive with skin metastasis nine and a half years after the second mastectomy.

The specific types and locations of independent primary nonmammary cancers following mastectomy are shown in Figure 3.

In Figure 4 the results of treatment of eighteen patients who had independent primary nonmammary cancers are presented. Most of the patients were over fifty years of age. The range of ages at the time the breast cancer was treated was thirty-four to eight-four years, the average being 56.2 years. In the patients in whom the independent tumor was not found at the same time as the mammary cancer, the time span between the first and the second ranged up to twelve years.

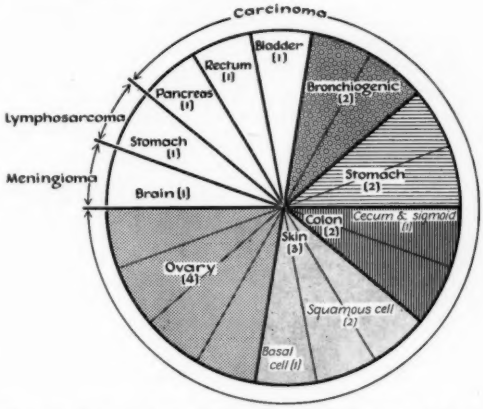

FIG. 3. Pie graph showing the specific types and locations of independent primary nonmammary cancers following mastectomy. Meningioma is included because tumor caused patient's death and was thought to be metastatic from breast.

The survival rate after diagnosis of nonmammary cancer was low: only six patients were living five years after the time of diagnosis, two of them with squamous cell cancer of the skin. Of the twelve patients who died, nine

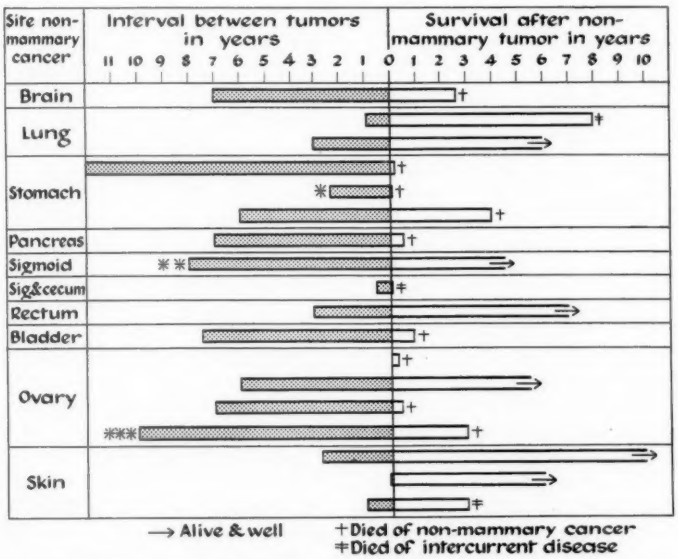

FIG. 4. Results in eighteen patients with independent nonmammary cancers following mastectomy for breast carcinoma. (Cases 1 to 18 reading from top.) → = Alive and well. † Died of nonmammary cancer. ‡ Died of intercurrent disease. * Included with bilateral simultaneous group also. ** Only male patient to develop nonmammary cancer after breast carcinoma. *** Only patient not autopsied.

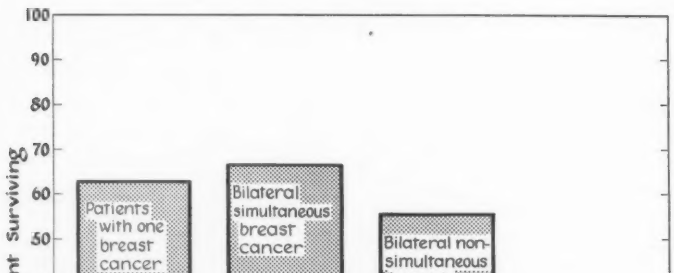

FIG. 5. A comparison of the five year survival rates of patients with one breast cancer and those with another malignancy following mastectomy is presented. There were seven patients in the bilateral simultaneous group but one had been observed for only fourteen months at the time of this report. There were eighteen patients in the independent primary nonmammary group but one had been observed only four and one half years at the time of this report.

died of nonmammary cancer all within five years of diagnosis of the lesion. Two died of nonmalignant cause (cerebrovascular and cardiovascular disease) before five years had elapsed, and one, of cerebrovascular disease eight years after the diagnosis of nonmammary cancer. In only one case was the possibility of recurrent breast cancer not definitely ruled out, autopsy not having been performed. However, it was the physician's opinion that the cause of death was ovarian cancer as there was no clinical or laboratory evidence of recurrent breast carcinoma.

In two cases the diagnosis of the nonmammary cancer or tumor was not made until necropsy. In one of them (case 1, Fig. 4) there was a thirty-two month history of vague complaints, mostly headaches, with some minor neurologic abnormalities eight months before death. As the patient had recurrent skin metastasis, the brain lesion observed in an x-ray film of the skull was assumed to be metastatic also. It is for this reason that this case is included in this study. In the other case (case 9, Fig. 4) laparotomy was performed and two independent primary malignant lesions of the bowel were found, one in the cecum and the other in the sigmoid. These were resected and no evidence of metastasis was observed. Two weeks later the patient died of myocardial infarction. At necropsy a small resectable unsuspected bronchiogenic carcinoma was found. No other evidence of carcinoma was observed.

There was one male patient who had a sigmoid carcinoma diagnosed eight years after mastectomy. He is still alive four and a half years after sigmoid resection and twelve and a half years after mastectomy.

A comparison of the five year survival rate of patients who had another cancer that developed after mastectomy, with the survival rate of 251 patients seen up to 1954 who had only one malignant mammary tumor is shown in Figure 5. (A total of 257 patients were treated up to 1954 for single breast cancer, but six were lost to follow-up and were not included.)

COMMENTS

The most important problem in dealing with a patient who has a lesion in the remaining breast after mastectomy is whether the lesion is metastatic or a new primary growth. In four of the seven cases of bilateral simultaneous lesions in the present study, the presence of the second lesion was not discovered until after one breast had been removed. Whether or not these four patients should be included with the

bilateral nonsimultaneous group is somewhat academic for the clinical problem remains the same.

The incidence of this phenomenon was higher in this series than is usually recorded for bilateral simultaneous breast cancer [*11*]. Hubbard [*12*] reported that in two of sixteen cases in which both breasts were removed, one of them prophylactically even though there was no palpable tumor in it, small cancers were found at pathologic examination of the prophylactically removed breast. Hoffman [*13*] recently reported a case in which a new primary cancer was found in the remaining breast four weeks after one breast had been removed. He believed it might have been present at the initial examination.

In the case of patients who are observed with a lesion in the remaining breast several months after mastectomy, making the correct diagnosis is equally critical. Harrington [*14*] pointed out the increased survival of these patients over those with unilateral disease. Allen [*15*] said that the incidence of a new primary cancer in the contralateral breast is greater than metastasis from the opposite breast. This was our experience in the present series—only four cases of metastasis to the contralateral breast in 355 cases.

Since the incidence of a new primary cancer in the contralateral breast is about 5 per cent, the advisability of prophylactically removing the uninvolved breast at the time of the first mastectomy or shortly thereafter is frequently discussed but doing so is not widely practiced. Dobson [*16*] expressed the opinion that the prophylactic removal of the uninvolved breast is justified in certain women, particularly premenopausal women with stage I disease and a family history of breast cancer. In our experience there was a strong family history of breast cancer in both the bilateral simultaneous and bilateral nonsimultaneous breast cancer groups. Five of the seven patients in the first group and six of the nine in the second group had a grandmother, mother or sister who had had breast cancer. An interesting phenomenon in our series was the occurrence of cancer of the left breast in each of premenopausal twins, the lesion in one patient developing within a month of that in the other. None of our patients had prophylactic mastectomy for reasons recommended by Dobson, although four had the remaining breast removed for cosmetic reasons and six because of pathologic conditions other than malignant. In a few instances multiple tumors were found in the same breast. Whether the origin of breast carcinoma is multicentric or not, surely there must be a biogenetic factor in the background. MacDonald [*17*] has emphasized the importance of biologic predeterminism in breast cancer.

The most challenging of the problems associated with postmastectomy patients concerns the development later of symptoms of a lesion in another organ. It is the more perplexing because so frequently it is a sign of distant metastasis and many of these patients are old and their symptoms are not clear either to them or to a physician. The circumstances may make for a long delay in establishing the diagnosis, hence the poor prognosis.

Moertel et al. [*18*] pointed out that a solitary lesion in the lung in a patient who has had one carcinoma need not necessarily be metastatic. We observed two patients who had pulmonary resection for cancer. One lived eight years after the operation and died of other causes. The other patient is still alive without recurrent disease six years after pulmonary resection and nine years after mastectomy. This argues for an aggressive approach in such cases.

Patients with intra-abdominal and pelvic lesions present problems in diagnosis and therapy. Laparotomy was performed in eleven such cases in the series, and in six of them a resectable lesion without gross metastasis was found. These six patients lived from two weeks to seven years, four of them at least four years. Five of the six ultimately died of nonmammary cancer; the other died of cardiovascular disease and a primary bronchiogenic cancer was found at necropsy. Gross local metastasis was observed at laparotomy in the remaining five of the eleven patients, all of whom died within a year of intra-abdominal or pelvic cancer. In this group there were delays in establishing the diagnosis and laparotomy was performed as an emergency in four cases.

Mider et al. [*6*] in a study of the incidence of multiple tumors, noted that the number of second tumors in patients with cancer of the breast or large bowel was greater than could be attributed to chance alone. They believed this was due to the increased possibility of the development of a second cancer of the same or similar histogenesis. The results of our study indicated that in patients who have had a mas-

tectomy for cancer of the breast there is about a 10 per cent greater than ordinary chance that another independent malignant neoplasm will develop. Some of the patients in our series who are alive may well develop another cancer. Statistically, fifty per cent of these second cancers will be in the contralateral breast and the other fifty per cent will be nonmammary. Hubbard found eighteen new cancers in 264 patients with a treated breast cancer. In nine cases the lesions were in the contralateral breast and in nine cases they were in other organs (three uterine, one ovarian, one gastric, one lingual, two epidermal and one sarcoma of soft tissue).

Kilgore and others [*19*] reported that twenty-one of 516 stage 1 breast cancer patients ultimately had cancer in the other breast and ten had cancer in other organs. However, these investigators did not state the number of second cancers in the 1,334 other patients reported in the same study. Elias et al. [*20*] found the incidence of multiple cancers to be 11 per cent in 730 postmortem examinations. We have one patient with three primary cancers and one patient with four independent primary cancers.

SUMMARY

In a review of 355 patients treated for cancer of the breast, it was noted that in about 10 per cent of them another independent primary malignant neoplasm developed after the first mastectomy. Bilateral simultaneous cancers were found in 2 per cent, bilateral nonsimultaneous breast cancers in 2.5 per cent, and independent primary nonmammary cancers in 5.4 per cent. The five year survival rate for patients with bilateral simultaneous breast cancer in this series was 66.6 per cent; for those with unilateral disease, 62.5 per cent; for those with bilateral nonsimultaneous breast cancer, 55.5 per cent.

The study indicated that patients in whom an independent primary nonmammary cancer develops after mastectomy for breast cancer have the poorest prognosis. The five year survival rate for this group was 35.3 per cent; and if the second lesion was an intra-abdominal or pelvic cancer the prognosis was even poorer, for early diagnosis of neoplasm at those sites was difficult. Data from this series suggested that the chance of cancers developing in the contralateral breast is about the same as that of development of an independent nonmammary cancer in patients who have had a mastectomy for breast carcinoma. In postmastectomy patients with a lesion in the remaining breast or another organ and in the absence of any evidence of distant metastasis, the new lesion should be treated as a new primary growth.

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DISCUSSION

IAN MACDONALD (Los Angeles, Calif.): By enlarging their study of multiple, independent neoplasms in patients with breast carcinoma to include extramammary sites, the authors have provided an excuse, if one was needed, to emphasize the genetic background of the capacity to develop cancer. The organ specific nature of the genetic influence is doubly apparent in the present study. The excess incidence of mammary cancer in the family background of these women is impressive: eleven of sixteen women with bilateral, apparently independent lesions had closely related females with cancer which was breast cancer. This is a genuinely significant finding, which I shall not be so naïve as to express in percentile estimate of only sixteen cases. But the comparison of relative incidence of mammary carcinoma to all cancer in the general population is only 11:100 in the United States, while the female relatives of the women evaluated by the authors as having had bilateral breast carcinoma had exhibited the neoplasm at an astonishing ratio of 69:100. That the two figures are not strictly comparable makes the comparison, in this instance, even more convincing, for we are comparing ratios of breast cancer to all cancer on the one hand, and breast cancer to all known relatives on the other. To my knowledge, this is the first time that a report on bilateral breast carcinoma has provided data on the family history of the disease. Previous data on familial occurrence in all cases of breast cancer have illustrated the increasing incidence of female relatives with mammary neoplasms proportionate to the completeness of genealogic information, as demonstrated by Madge Macklin. Most American reports, including one of mine, report no more than 40 plus per cent of mammary cancer to all cancer. European studies as done by Wassink, Waaler and Martynova, in Holland, Norway and Russia produced familial mammary cancer to all cancer ratios of up to 60 per cent. An equivalent figure was reported by Macklin when she investigated families resident for several generations in stable communities in Ohio and adjacent states.

It would be of extraordinary value to determine the ratio of familial mammary cancer to all cancer for the cases of bilateral breast cancer reported today; unless there are unusual and unlikely differences present, the selective determinism of their relatives for breast cancer should approach that of laboratory animals genetically manipulated to produce mammary carcinoma in over 90 per cent of litter mates.

Further evidence of the genetic background of mammary carcinoma is that of the thirty-four women in this study another breast carcinoma developed in almost half of them as their second neoplasm. Actually, a more exacting comparison would be possible if certain nonmammary neoplasms were excluded for one reason or another. The three instances of cutaneous carcinoma are examples of predisposition of local tissue to a mutant influence in the environment (i.e., actinic radiation, which assumes that these three patients were nonresidents of San Francisco!). Cerebral meningioma and gastric lymphosarcoma are examples of neoplasms far removed from mammary carcinoma in their histogenesis, natural history and, probably, in etiology. There remain only thirteen patients in whom independent, visceral cancer of epithelial origin developed. Assuming the validity of this exclusionary reasoning, the proportion of independent, nonmammary neoplasms to mammary primary, second lesions becomes as 13:16, or a predeliction toward a second breast lesion in the ratio of 55:45, rather than of 11:89 as in the general population.

From all of this I suggest that there emerges a consideration of practical importance. It has been my conviction that the attitude of those surgeons recommending routine, prophylactic simple mastectomy supplementary to contralateral radical mastectomy for carcinoma represented the triumph of action over reason. This was supported in a report by Guiss before this Association in 1954 when he demonstrated that, to have altered the outcome in seven patients with nonsimultaneous, bilateral disease would have required a total of 925 "prophylactic" simple mastectomies. Otherwise expressed, 918 useless procedures would have been performed for the benefit of seven patients. In a discussion of this report, Dobson suggested a limitation of such "prophylaxis" to stage 1 cases, while Seabrook saw no justification for it. The essayists of this session have turned up a valid criterion, I believe, for the application of ablation of the opposite breast, i.e., a family history of mammary carcinoma, especially in those whose mother, grandmother (maternal or paternal) or sister have been so afflicted.

For the sake of consistency if nothing else, I shall close criticizing only one aspect of this excellent paper—the implied devotion of the authors to the importance of "early" treatment, not otherwise qualified. If I may be anecdotal, about 1944 I performed a radical mastectomy on a woman of

Amazonian proportions, of lipomatous rather than muscular extent. The primary lesion was 7 cm. in diameter, else it would not have been palpable within the impressive mass of mammary fat. Six months later I discovered another three dimensional mass in the opposite breast almost as large, which I had obviously overlooked in my obsession with the opposite lesion. The patient resisted any suggestion of action for four years, during which time the second tumor increased in size from 5 to 8 cm. When, with the patient's increasing obesity, the nipple was roughly in line with the umbilicus, I was permitted to perform a simple mastectomy only. In 1958 death, as it must to all, came to this overfed and undernourished woman, fourteen and ten years after the treatment of bilateral mammary carcinomas, both of which were late and large.

LEONARD G. DOBSON (San Francisco, Calif.): When a patient with cancer of the skin is kept under observation I think most of us realize that there is a great possibility of finding another carcinoma of the skin sooner or later. When we are following the course of a patient who has had a radical mastectomy, many of us are of the opinion that there will be at least a 5 per cent chance—one chance in twenty—of that patient developing another carcinoma of the other breast within the next ten, fifteen or twenty years.

This paper brings out the important point that there is an equally high, maybe a slightly higher, incidence of a new carcinoma arising in other organs. Its lesson, therefore, is to be especially on the alert for new carcinomas and to insist on the cooperation of patients in their having fairly frequent follow-up examinations after they have had one carcinoma either of the breast or of other organs.

The additional lesson that I learned from this paper was that we should make a more energetic attack on these new carcinomas because, as Dr. Kountz points out, there were several that were primary carcinomas and not metastases and, therefore, we cannot assume that a new lesion or an apparently new lesion is a metastasis and not a new cancer. Six or seven of these patients would not have been cured had that assumption been made.

ALBERT C. DANIELS (closing): Of these 355 cases, to date, only six have been lost to follow-up. One autopsy was not obtained; otherwise, all deaths were documented.

The keeping of records shows how our memories can play tricks. The problem of bilateral malignancy came up when one of our surgeons was operating on a cancerous breast, and one of the house staff called his attention to a lump on the other side. He biopsied the second tumor and found it to be malignant also. He was confronted then with what to do with two malignancies, and he stated that this was the first time this had ever come up in his practice.

When we reviewed the data there were two other of these simultaneous cases which had been operated on by this same surgeon. The years go by and one forgets what has happened. But with tumor boards that review these cases from year to year and refresh our minds, we certainly learn more about the treatment of cancer.

The Treatment of Breast Cancer

I. A CRITICAL APPRAISAL OF THE EN BLOC PRINCIPLE AND THE ROLE OF RADICAL MASTECTOMY

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THE purpose of this paper is to present a retrospective study of the treatment of breast cancer by radical mastectomy at the University of Oregon Medical School Hospitals and Clinics during the fifteen year period 1940 to 1955 and to assess the validity of the traditional *en bloc* principle of cancer surgery in the context of that clinical experience.

MATERIAL AND METHODS

The present study is an analysis of 204 consecutive cases. A final evaluation of this clinical material was made February 1, 1961. Thus, there is a five to twenty year follow-up of patients. All clinical diagnoses were confirmed by histopathologic study.

The series does not represent all patients with breast cancer seen in the Tumor Clinic and treated at the University of Oregon Medical School (UOMS). To illustrate this point, the distribution of all breast cancer patients treated during representative years 1950 to 1951 is shown in Table 1.

Selection of Cases. The clinical criteria of operability that governed decisions of the Tumor Board were more liberal than the Haagensen criteria [*14*]. The size of tumor and clinical staging in combination were not considered absolute determinants. Adverse local signs, except for the occasional fulminant and unquestioned inflammatory carcinoma, did not negate primary radical mastectomy. Nor did pregnancy, by definition, preclude operation. Once a clinical judgment of operability had been reached, the patients were hospitalized at the teaching hospital. The rotation of service assignments in hospital of visiting staff surgeons and the closely integrated activities of full time surgeons led to a randomization of treated patients at this point. A precise definition of the technic and the extent of so-called radical mastectomy was not established as a fixed operational policy. Thus, distinctive differences in surgical philosophy and operative technic were reflected in the treatment of the individual patients. The traditional conservative and radical positions of surgery in relation to the operative treatment of cancer were represented. A study of the two contemporary series which resulted are the basis of this report. It is essentially a comparison study of conservative or conventional radical mastectomy [*22,47*] and extended ultraradical mastectomy in the surgical tradition of Halsted [*11,16*].

TABLE 1
RATIO OF PATIENTS TREATED IN SERIES TO THOSE TREATED AT UOMS, 1950–1951

Ratio	Treatment	No. of Patients Over-all
1:2	Primary radical mastectomy, UOMS, operable breast cancer	33
1:4	Mastectomy performed elsewhere, admitted for evaluation and palliative therapy (x-radiation and endocrine manipulation), advanced breast cancer	16
1:10	Simple mastectomy, UOMS, palliative operation, or high-risk geriatric patient	6
1:15	X-radiation therapy only, advanced breast cancer	4
1:20	Terminal care, carcinomatosis	3
	Total	62

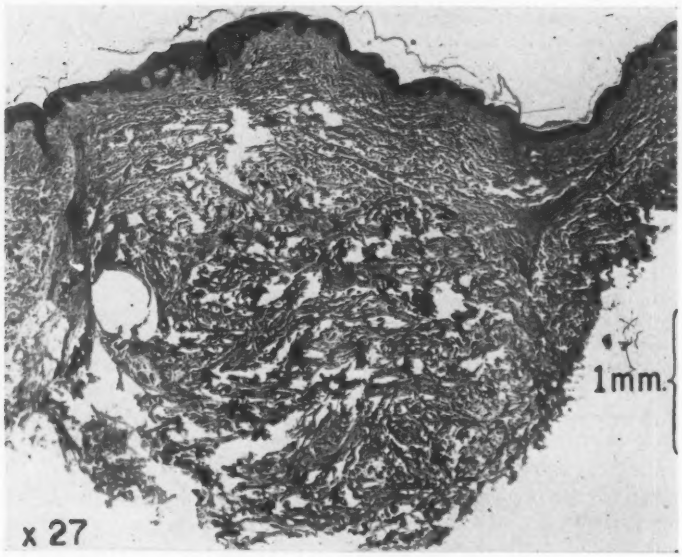

FIG. 1A. Dermal lymphatic metastases. Original magnification ×27.

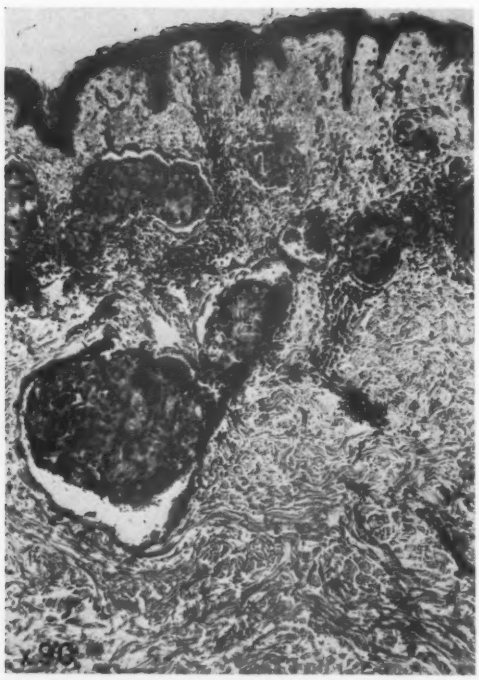

FIG. 1B. Dermal lymphatic metastases. Original magnification × 90.

Series A and Series B. The two comparison series will be designated at this time as Series A and Series B. It is important that we should emphasize the retrospective basis of this identification: the two series were not established on an anterospective basis. The random assignment of patients with operable breast cancer occurred in hospital following the establishment of operability by action of the Tumor Board, and one of two possible operative events then took place.

The fundamental differences between the two groups will be apparent from a brief description of prototypes of the two surgical approaches:

Series A: After the decision of the Tumor Clinic had been made, biopsy or biopsy excision diagnosis under general anesthesia was followed by what we will call a *standard radical mastectomy*. In general, the parameters of the *en bloc* dissection were more limited, the skin flaps thicker, the axillary dissection less meticulous, and seldom carried over the elements of the brachial plexus. The axillary vein might be skeletonized, but more often than not, this was not undertaken. The long thoracic and thoracodorsal nerves were invariably preserved. An immediate skin closure was accomplished by primary suture, frequently under some tension, and retention type sutures

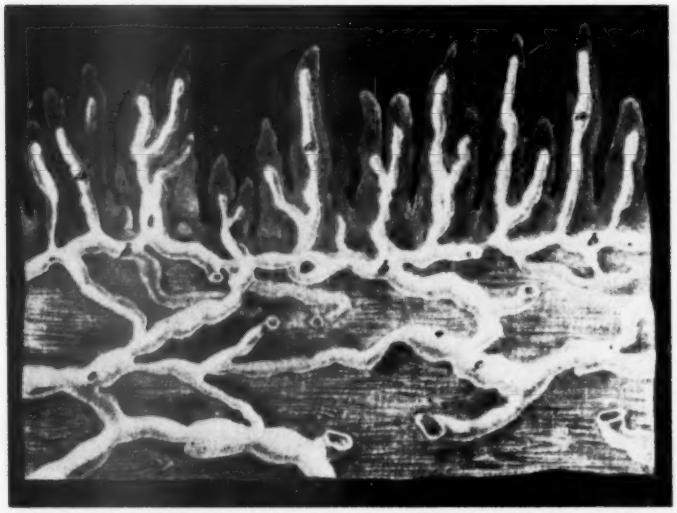

FIG. 2. A structural basis for lymphatic spread of cancer. (From: TEICHMANN, L. The capillary lymphatic vessels of human skin. In: Cancer of the Breast and Its Operative Treatment [12].)

were used to sustain the wound closure. At the time of a preliminary review of the two series (1952), average operating time in the first fifty Series A patients was 107 minutes. The incidence of lymphedema was less, but the frequency of wound infection was increased 2:1 over the Series B patients.

Series B: After a Tumor Clinic decision of operability had been made, biopsy-excision (more frequently than biopsy) for diagnosis was followed immediately by an *extended radical Halstedian mastectomy*. The operative technic of Haagensen [16], with several notable exceptions, has characterized the treatment of Series B patients and been the basis of our surgical resident teaching. Modifications in the ultraradical operation that we have made are based on the following considerations:

1. The significance of the dermal lymphatics in relation to the clinical problem of local persistence of carcinoma following mastectomy led us to an early abandonment of the thin skin flap dissection of Haagensen [16] and Auchincloss [58], rather than to a revision of the criteria of operability. The combined evidence from histologic studies (Figs. 1A and 1B) in recurrent cases, the clinical patterns of local persistence, the gross, microscopic and functional anatomy of the lymphatic apparatus (Figs. 2 and 3) all serve to emphasize the paramount role of the lymphatic system in the development of local metastases. Moreover, the dissection of extremely thin skin flaps (several millimeters or less) is time consuming and ischemic necrosis occurred not infrequently. For these reasons, the anatomically fallacious (Fig. 4) and tedious thin skin flap dissection was abandoned.

2. We have sacrificed increasingly large areas of skin and soft tissue from the chest wall. At the present time, average skin replacement for the defect resulting from extended radical mastectomy approximates 400 to 500 cm. [2]. The high incidence of dermal persistence following limited *en bloc* excisions for carcinomas of the upper outer quadrant leads us to make no compromise with breast cancer in this most common location. As a necessity we have developed the operative technic of a deltoid skin sliding full thickness skin graft to accomplish immediate coverage of the exposed axilla in the axillary skin short case. This maneuver is illustrated in Figure 5A and B. To increase the likelihood of uncomplicated wound healing to an optimum, we have replaced the technic of primary skin grafting at the time of mastectomy by delayed skin grafting. The delayed graft technic obviates the occasional problem of a primary graft loss due to incomplete hemostasis and seroma formation beneath the graft. At the time of delayed grafting (forty-eight to seventy-two hours after radical mastectomy) immediate debridement of medial or lateral skin flap can be undertaken if there

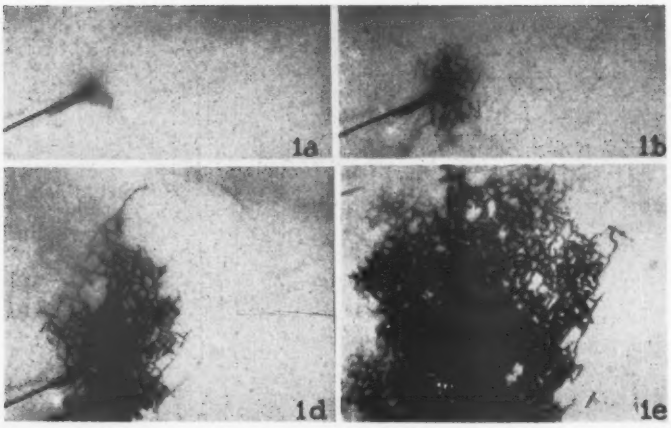

FIG. 3. Functional anatomy of the dermal lymphatics (intravital dye injection). (From: MCMASTER, P. D. and HUDACK, S. *J. Exper. Med.*, 56: 239, 1932 [36].)

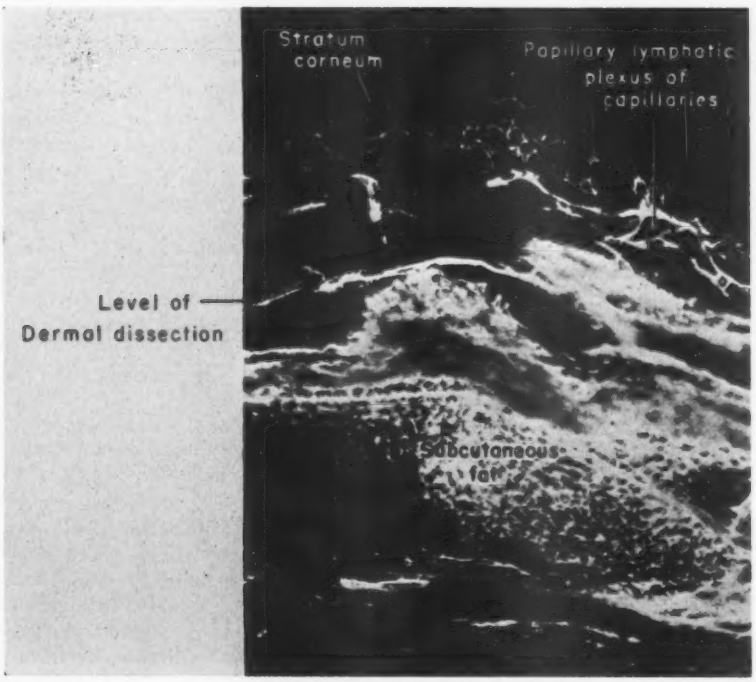

FIG. 4. The relation of lymphatic vessels to the spread of cancer demonstrated by injection studies, suggesting the fallacy of dermal dissection. (Adapted from: GRAY, J. H. *Brit. J. Surg.*, 26: 462, 1938 [28].)

is evidence of ischemic change. The inevitable wound sepsis that follows unrecognized ischemic necrosis and wound slough is avoided. The medial and lateral skin flaps are fixed firmly to the chest wall by the time of delayed skin grafting. The incidence of complete graft takes is increased. The management of the axillary space is simplified.

3. Influenced by our studies of perineural lymphatic extensions of breast cancer and the occurrence of brachial plexus pain syndromes in the group not cured by radical mastectomy

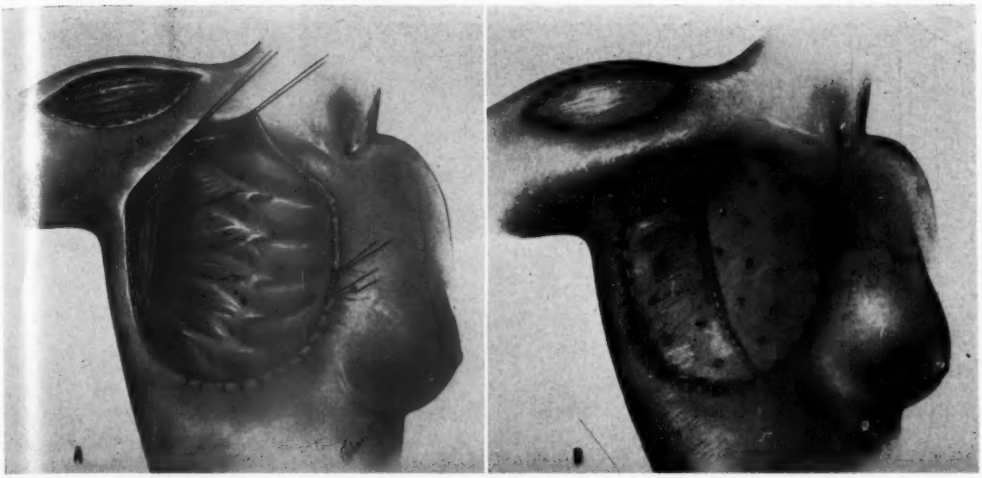

FIG. 5. Deltoid skin sliding full thickness skin graft and delayed split thickness skin graft for axillary skin short cases.

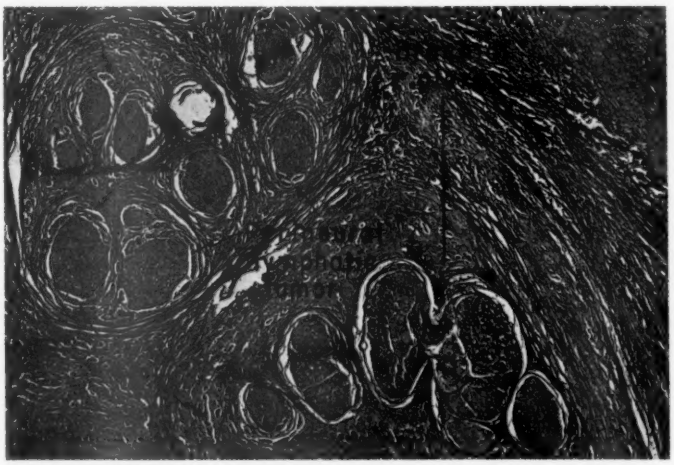

FIG. 6. Incurable breast cancer, extensive perineural lymphatic invasion, brachial plexus compression pain syndrome (postmortem material). Original magnification ×29.

(Fig. 6), we have sacrificed the long thoracic nerve and/or the thoracodorsal nerve in a high percentage of cases. The functional limitations that result from this procedure have not been sufficient to cause us to reverse it. A more complete *en bloc* operation is the gain.

Average operating time in the first fifty Series B patients was approximately 300 minutes. Operating time has decreased significantly since the thin skin flap dissection was abandoned for an increasingly wide excision of skin and soft tissue.

Under these conditions, average hospital stay for the two series is comparable. The results that will be presented reflect the surgical philosophies of two schools of surgeons, rather than individual operative technics. Thirty surgeons (visiting surgeons, full time staff surgeons and surgical residents in training) were responsible for the first hundred

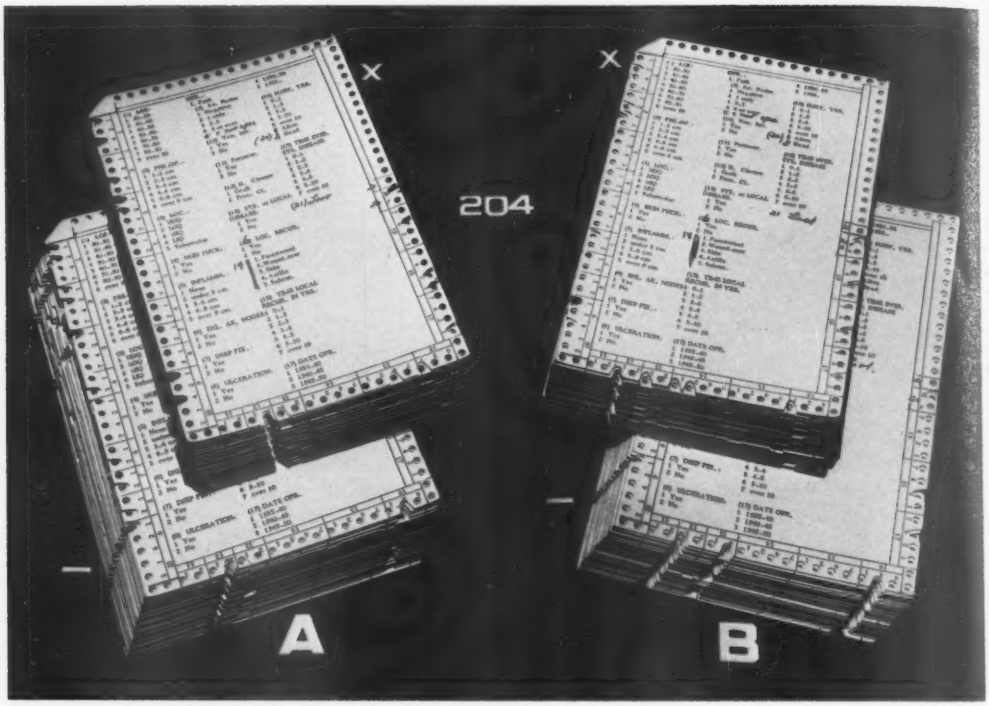

FIG. 7. The raw data assembled on punch cards.

cases, which illustrates this point. The operative mortality for the total series of 204 patients was 2.0%. There was one death in Series B patients (an Rh transfusion reaction with renal shutdown), an operative mortality of 1.1%.

Analysis of Data. The clinical information from the total series of 204 patients was transferred to punch cards. Cross correlations were then possible with reference to some twenty different factors. (Fig. 7.) The Series A (conventional radical mastectomy with primary skin closure) group was distinguished, at this time, from the Series B (extended radical Halstedian mastectomy with wide skin excision and skin graft) group by a single criterion of radicability: the necessity for skin grafting. Gilchrist [*20*] and Monroe [*29*] have indicated another test of radicability, the total extent of the *en bloc* resection as determined by a node count of the operative specimen. Haagensen has indicated the relation between operating time and operative procedure [*48*]. The two major series, A and B, were then subdivided into series A−, A+, B− and B+ on the basis of pathologic grading. A series of comparisons and cross correlations will be made within these four clinical groupings. Finally, the confidence limits for differences in local recurrence rates and survival between the four comparison series will be established by generally available statistical methods [*63–67*].

Comparison of Groups. As an introductory step in the analysis of data, a search was made for lack of homogeneity or evidence of bias. The demonstration of sampling error would invalidate any statistical evaluations that might be made of the four different series. The major distinction between Series A and Series B groups still allows for a wide variance in the individual case. Series size is sufficient so that individual variance on this basis will probably not show in the total series. The subdivision into Series A−, B−, A+ and B+ introduces a factor of some significance. Bloom [*44*] has indicated that a classification for breast cancer which depends upon either staging or grading tends to group cases not strictly

TABLE II
SIZE OF PRIMARY CANCER

Series	Number of Patients	Arithmetic Mean Index*
A−	58	2.78
B−	39	3.07
A+	57	3.56
B+	50	3.98

similar. He suggests the linking of grading and staging. It is well established that pathologic staging is open to error of several types (missed node involvement; pathways of invasion, such as the parasternal nodes, not presently considered in our system of staging). For obvious reasons, an error in staging will be adverse to both Series A− and B− groups. Evidence for homogeneity of the different series can be developed from an analysis of several important factors: size of the primary lesion, incidence of axillary node involvement, and age of patients. These factors have been reviewed and the data presented in Tables II to IV.

It is difficult to establish a positive correlation between age of patient and prognosis for survival. A careful analysis by Shimkin et al. [*55*] led them to conclude that it could not be demonstrated. Smithers [*46*] has stated that the force of mortality in breast cancer is dominant for age fifty to sixty (cf. arithmetic mean age index of 4.0). Lewis and Rienhoff [*61*] observed a significantly lower mean and percentile survival in younger than in older women with a consistent increase in mean survival with advancing age. From our data we would conclude that the differences in age indexes are of minimal significance, particularly in those

TABLE IV
AGE OF PATIENT

Series	Number of Patients	Arithmetic Mean Index*
A−	58	5.07
B−	39	4.61
A+	57	4.62
B+	50	3.75

* The mean indices for size and age of patient were derived from the punch card data (Fig. 7) and are arithmetic mean determinations for the individual series. Thus, an index of 3.0 = 3 to 4 cm.

TABLE III
INCIDENCE OF AXILLARY NODE METASTASES

Series	Number of Patients	Pathologic Stage 2
A	115	48.7%
B	89	56.2%

series which have the greatest interest (A− and B−).

The cross correlations between size of tumor and incidence of axillary node metastases suggest a sampling bias adverse to the B series. There is an alternative explanation, however, which invokes the explanation of biologic indolence of the larger tumors. A reversal of interpretation would be necessary, if this explanation were to be supported by facts. A further comparison was necessary to test this possibility. The data is summarized in Table V.

There is no basis for correlating large tumor size with low tumor virulence and metastasizability. It would appear that large tumor size correlates with an increased incidence of axillary node metastases. Individual exceptions are almost the rule, of course, with so capricious a disease as breast cancer.

In summary, the relative homogeneity of the four clinical series, A−, A+, B− and B+, seems to have been established at a reasonable level of confidence. There is a suggestion of bias that is generally adverse to the Series B group of patients.

Sample Size. The total series of 204 cases with four comparison series of an approxi-

TABLE V
SIZE OF PRIMARY CANCER AND INCIDENCE OF AXILLARY NODE METASTASES

Series	Number of Patients	
	Arithmetic Mean Index Less than 4.0	Arithmetic Mean Index Greater than 4.0
A−	41	18
A+	28	28
(18/46 A−, 39.1%)		
B−	25	13
B+	20	31
(13/44 B−, 29.8%)		

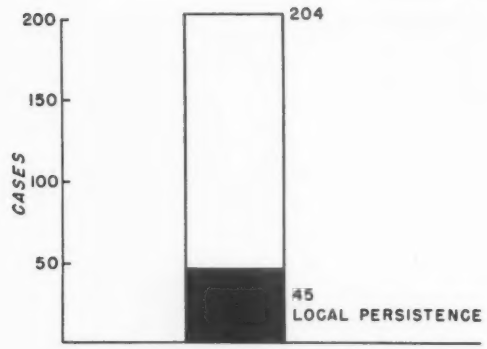

FIG. 8. Local persistence in total series.

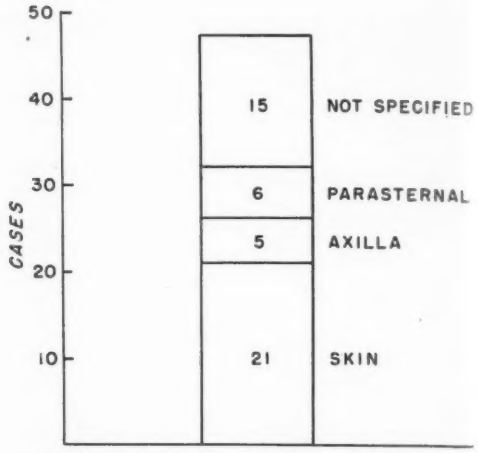

FIG. 9. Local persistence after radical mastectomy.

mately similar size provides individual series that are sufficiently large for general statistical analysis.

RESULTS

Results of the analysis of the comparison series (standard radical mastectomy with primary skin closure versus extended radical mastectomy with wide *en bloc* skin excision and wound coverage by delayed skin grafting) will be presented in two sections: Local Recurrence, and Prognosis for Survival.

LOCAL RECURRENCE

There were forty-five cases of local persistence in the total series of 204 patients. (Fig. 8.) A general classification of local metastases is shown in Figure 9. There is a parallelism between our observations and those of surgeons who have previously reviewed the problem of local persistence after mastectomy [*55–62*]. If there is lack of agreement on a strict definition of the term, there is unanimous agreement that local recurrence is an indication of failure of the *en bloc* procedure. The mechanisms of local recurrence following *en bloc* operations are classified as follows: (1) Local metastases or dermal persistence from an incomplete *en bloc* operation; the mechanism of spread is lymphatic for the most part; the role of the circulating cancer cell [*38,39*] and blood vascular embolization in relation to local metastases seems extremely remote; (2) retrograde spread from intercostal or internal mammary lymph node metastases with secondary dermal parasternal involvement [*58*]; (3) axillary recurrence, which may be both dermal and axillary lymph node persistence, from an incomplete *en bloc* operation and axillary lymph node dissection;* (4) tumor cell transplantation to the operative wound, or the donor site, as an autologous transfer.

Patterns of Recurrence. *1. Local metastases or dermal persistence* was located characteristically in the wound scar or in a centrifugal pattern of spread [*12*] around the wound scar (Series A patients); or at the periphery of the skin graft in recurrences in Series B patients. The predominance of primary breast cancers are upper outer quadrant lesions (117 of 204 in this series) and dermal persistence was highest in both Series A and Series B patients in relation to upper outer quadrant lesions. Local metastases presenting as dermal persistence were of lowest incidence in lower outer quadrant primary breast lesions. It is significant that six of twenty-five primary lesions that were subareolar were followed by local persistence—all of them in Series A patients. There were twenty-one cases of dermal persistence, six in Series B patients and fifteen in Series A patients.

2. Parasternal persistence was the dominant type of recurrence in grafted cases of Series B. The inner quadrant (upper inner quadrant or lower inner quadrant) primary breast cancers were found in thirty of 204 patients. There is the suggestion from this that the problem of internal mammary node extension is unresolved.

* In 1894, Halsted said of supraclavicular metastases: "Hereafter, we shall consider supraclavicular recurrences as local."

3. Axillary recurrences were dermal, nodal or combined. Axillary node recurrence was a complication of limited operations. The same cannot be said for axillary dermal persistence. The deltoid skin shoulder sliding full thickness graft which was devised for the high upper outer quadrant lesion has been used in perhaps twelve or fifteen patients in the last five years and does not affect the recurrence results in the 1940 to 1955 series under review.

4. Implantation metastases beneath an extensive skin graft without peripherally located dermal metastases were observed in several patients with advanced breast cancer treated by radical mastectomy.

Time of Recurrence. The time appearance of local recurrence suggests a log normal function and has implications for prognosis that are unfavorable. The majority of local recurrences are manifest by five years [59] and the median local recurrence time for the University of California series was eighteen months [55]. Our series followed this general pattern. Only two of forty-five local recurrences occurred at more than five years after operation. More than 90 per cent of local recurrence in our series was clinically evident by three years after operation.

Size of Primary Carcinoma. An increase in tumor size and the existence of axillary lymph node metastases correlated with an increased rate of local recurrence after operation. The data for Series A+ and B+ are summarized in Table VI.

TABLE VI
LOCAL RECURRENCE IN RELATION TO SIZE OF PRIMARY CANCER

Recurrence and Nonrecurrence	Arithmetic Mean Size Index
Series A+	
Local recurrence.....	4.12
Nonrecurrence.....	2.91
Series B+	
Recurrence	4.21
Nonrecurrence.....	3.74

Significance of Axillary Metastases. The staging of tumor is a most significant factor in prognosis. In this series of 204 cases, the incidence of local recurrence was increased by a factor of tenfold. The over-all rate of local persistence was 22.5 per cent of cases: 2.5 per cent for pathologic stage I cancers; 20 per cent for stage 2 carcinomas. It would seem more reasonable to relate the apparent recurrence rate in stage I cancers to errors in staging, rather than to consider it the rate of circulating cancer cell local metastases.

Extent of the En Bloc Operation. A highly significant correlation is evident from the data that are summarized in Figure 10. This information is presented again in Table VII.

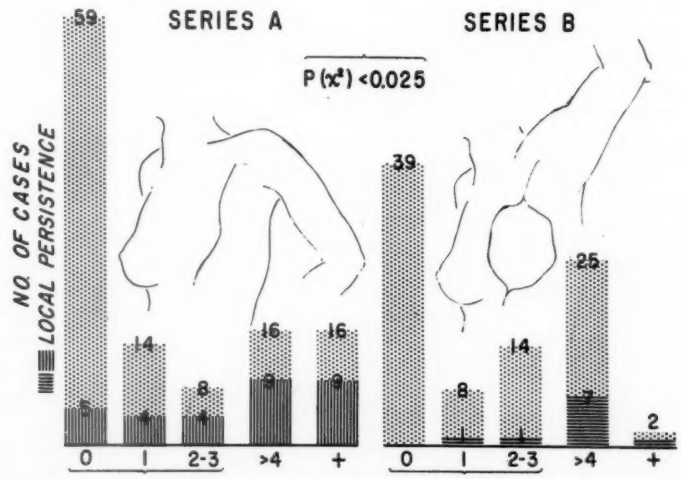

FIG. 10. Axillary node involvement.

TABLE VII
LOCAL METASTASES IN RELATION TO EXTENT OF THE EN BLOC OPERATION

Series	Number of Patients	Local Recurrence Rate (%)
A−	58	8.4
A+	57	45.6
B−	39	0.0
B+	50	28.0

When the extent of the *en bloc* operation and a quantitative expression of axillary node metastases are linked, so that stage I cancers and relatively minimal involvement as axillary metastases (low density axillary tumor) are compared, a highly significant relationship is demonstrated in the chisquared test. A calculation was made for Series A+ and Series B+ groups, excluding high density (4+) axillary node metastases cases, and including all of the Series A− and B− groups, as well. The following data were used in the calculation:

Series	Local Recurrence	No Local Recurrence	Total
A	12	67	79
B	2	59	61
Total.....	14	126	140

Calculation of $x^2 = 5.424$
df 1, $P(x^2)0.01–0.025$

A 95 per cent confidence limit is expressed. A statistical inference is justified when P is 0.05 [63]. The superiority of the extended *en bloc* operation (Series B) is verified by this comparison study. The high rate of local recurrence in both series A+ and B+ in advanced breast cancer indicates that the limits of curability of the tumor by the *en bloc* procedure has been exceeded.

Selection of Operation. These general observations and cross correlations fail to provide a basis for the individualization of operative procedures in the treatment of operable breast cancer. The individual exceptions and clinical errors in staging, lack of a biologic test of tumor virulence, metastasizability and implantability, and evidence that early tumor extension beyond the breast is the rule rather than the exception [35,45,53], are considerations that influence us to carry out the widest possible *en bloc* operation in each patient with operable breast cancer.

TABLE VIII
A CORRELATION OF TUMOR SIZE, STAGING AND LOCAL RECURRENCE

Number of Patients	Size of Carcinoma (cm.)	Axillary Node Involvement					Stage I Local Rec.		Stage 2 Local Rec.	
		0	1	2–3	4+	+	Yes	No	Yes	No
19	1–2	14	0	0	3	2	0	14	0	5
37	2–3	23	3	2	8	1	1	22	4	10
46	3–4	25	5	5	8	3	0	25	6	15
49	4–6	21	6	7	12	3	2	19	14	15
25	6–8	6	5	6	5	3	1	5	7	13
16	8+	4	1	1	6	4	1	3	9	3
12	Not specified	3	. .	...	...	9	...	...	...	...

Some further correlations are assembled in Table VIII and Table IX.

Local Recurrence and Curability. All forty-five patients in this series are dead or dying of disseminated cancer. Oliver and Sugarbaker [57] discussing the significance of recurrence following radical mastectomy emphasize that dermal recurrence by any route implies true metastases. Warren and Tompkins have attached the same significance to local recurrences after operation. The University of California group observed that the difference in mean survival of patients with osteolytic metastases and with local recurrence was not significant in that series [55]. With all of these authors we agree. In discussing the treatment of advanced breast cancer, Gilchrist suggests the possibility of late central vein invasion of

TABLE IX
A CORRELATION OF TUMOR SIZE, STAGING AND SURVIVAL

Number of Patients	Size of Carcinoma (cm.)	Total Series, Axilla −		Total Series, Axilla +	
		Cancer Free	Dead or Living with Cancer	Cancer Free	Dead or Living with Cancer
19	1–2	14	3	1	1
37	2–3	21	3	5	5
46	3–4	22	3	6	8
49	4–6	18	3	5	16
25	6–8	5	0	2	12
16	8+	5	1	1	10
12	Not specified	...	...	...	...

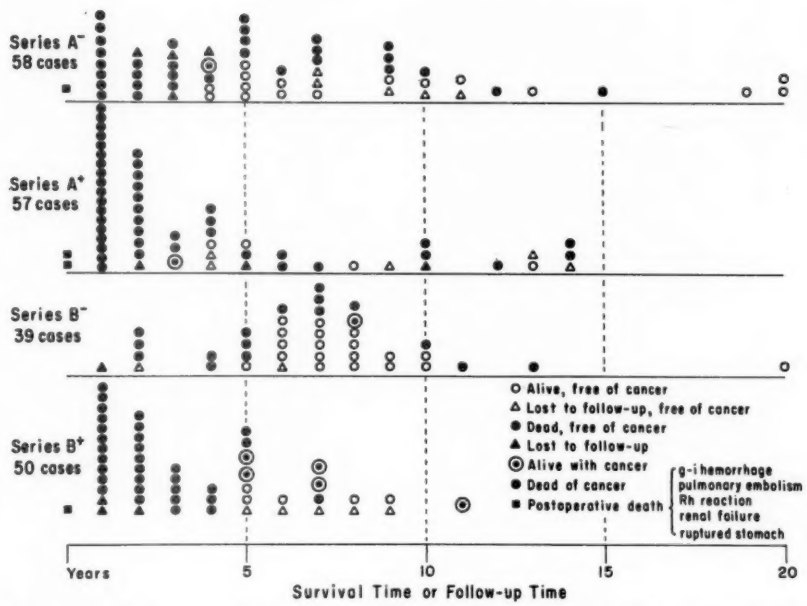

FIG. 11. A dot diagram of survival time and follow-up time in a continuing series (204 cases from 1940 through 1960), showing the clinical results after conventional radical mastectomy (Series A) and extended radical mastectomy (Series B) in pathologic stage 1 (−) and stage 2 (+) breast cancer.

lymph nodes to explain widespread metastases as long as ten to thirty years after operation. A similar state of dormancy may apply to local metastases. There is evidence that the lymphatic milieu is favorable to the free-floating cancer cell [*26*], even more favorable than the blood vascular system [*38,40*]. Dormant local metastases may serve as a focus of spread and eventuate in generalized metastases. We have observed this visible sequence of events in uncontrolled breast cancer in the anterior chest wall. We agree with Pickrell et al. [*62*] that the distinction between local recurrence and metastatic cancer is an arbitrary one. It is necessary to show an improved survival rate from extended *en bloc* operations before this association and its implications for therapy have complete significance. In the section that follows, this question will be reviewed again.

PROGNOSIS FOR SURVIVAL

Presentation of Clinical Results. A general picture of clinical results in the total series of 204 cases and each of the four series (A−, A+, B−, B+) is shown in Figure 11, a dot diagram of survival time and follow-up time after operation. This composite representation of information will serve for the calculation of crude five year survival rate (Table x) which may be compared to similar statistical reporting for other series [*48,50,52*], the more accurate actuarial figure, expectation of life, or maximum likelihood estimate of long-term survival rate [*65*]. As Boag [*64*] has emphasized, such a presentation of all of the information in the data will permit statistically valid comparisons

TABLE X
UOMS BREAST CANCER SERIES: CRUDE FIVE TO TWENTY YEAR SURVIVAL RATES

Series	Number of Patients	5–20 Yr. Survival (%)
B−	39	82.1
A−	58	56.9
B+	50	36.0
A+	57	29.8

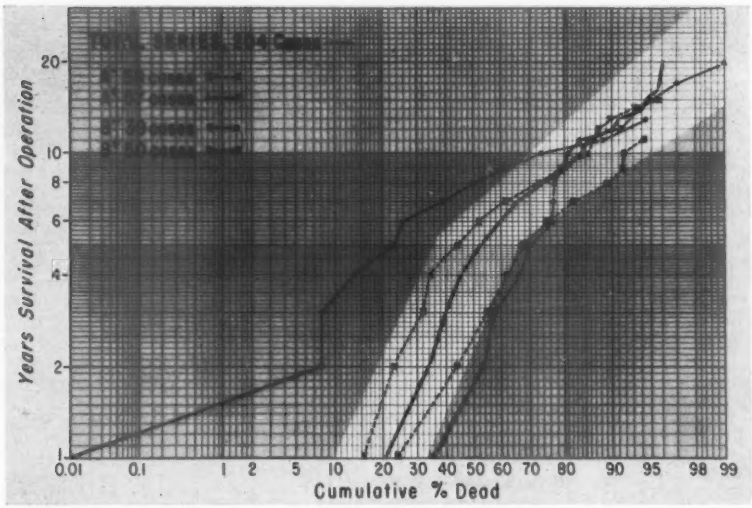

FIG. 12. Duration of survival after operation for cancer of the breast in four clinical series (1940 through 1960), shown as a plot of log probability paper. A 95 per cent confidence limit for these survival data are indicated by the unshaded part of the graph.

of the results of different investigators, whatever statistical method of analysis is used.

Statistical Analysis. A simplified "maximum likelihood" estimation method [*66,67*] was used for the analysis and comparison of total survival data. This statistical method is especially valuable when some patients are still living at the time of reporting. In spite of some obvious statistical qualifications,* the maximum use was made of available information and a statistical analysis on a comparison basis was made.

Results. The duration of survival after operation in the various groups (A−, A+, B−, B+) is shown in Figure 12 as a plot on log probability paper. The peculiar distribution of the survival data in each of the four series suggests that two populations of patients are represented in the composite log plot for each series. This most likely represents a combination of (1) a breast cancer death curve and (2) a survival curve for risk of dying exclusive of breast cancer (or natural life expectation). Simmons' studies of late results of operation show that late recurrence developed in most instances in patients who had pathologic stage 2 breast cancers.

The statistical evidence from our study is highly significant in the following respects:

1. Series B− patients demonstrated a superior survival time over all other groups (confidence limit 99 per cent) and for at least ten years after operation. The log mean survival time (the time for 50 per cent of the patients to die) was eight years.

2. Series A+ patients demonstrated a poorer survival time than all other groups (confidence limit 95 per cent). The log mean survival time was 1.6 years.

3. The data was inconclusive in separating the A− series and B+ series from the log probability curve for the total series. Log mean survival time (Series A−) was 5.6 years; log mean survival for Series B+ was 2.5 years. The mean survival time of untreated breast cancer has been reported to be approximately thirty-eight months [*55*]. The crude five year and ten year survival rates for collected series of untreated patients with breast cancer [*69,70*] permit rough comparisons with the survival data of our series.

COMMENTS

These data provide definitive information.

* A control series of untreated, randomly selected breast cancer cases will probably never be established. The baseline data for untreated breast cancer is collected in a few references [*68–70*]. The date of onset of malignancy is impossible to establish. An absolute 100 per cent follow-up is improbable for any series.

The superiority of well devised and well executed *en bloc* cancer operations on the principles laid down by Halsted three quarters of a century ago [*11*] is reaffirmed. This conclusion is supported by the comparison study of local recurrence after *en bloc* operations of variable scope. The data suggest that a significantly increased mean survival time and a decreased rate of local recurrence will follow the use of extended radical mastectomy with wide *en bloc* skin excision. There is positive evidence, also, that the extended radical operation does not reduce survival time in the incurable patient (cf. Series A+ and Series B+) if clinical cure is not realized. We are satisfied from our clinical experiences with palliative therapy through fifteen years of tumor clinic work [*54*] that closed carcinoma, as Sir Stanford Cade has termed it, is infinitely preferable to open, infected, ulcerating, fungating, eroding, local cancer persistence. Surgeons should not be influenced by criteria of inoperability to exclude palliative operations [*62*] and it is our clinical opinion that the extended radical mastectomy which fails to cure may yet be the better palliative operation.

In the light of such evidence, it is difficult to justify retrogressive moves in the treatment of breast cancer which go backward in time to the days of Billroth versus Eiselsberg and other pre-Halstedian surgeons, when the cure of breast cancer was unknown and the "recurrence" rate was 60 to 100 per cent within a few months after operation [*13*].

The contemporary trend to experiment with the individualization of treatment for operable breast cancer is particularly distressing when simple mastectomy is used in the treatment of stage 1 breast cancer. We are led to conclude that an extended radical mastectomy on the *en bloc* principle with wide skin excision is the operation for many rather than, as has been said, for the few: "For example, mortality statistics indicate that we may expect to see approximately 50,000 new cases of breast cancer each year. If 25,000 of these are pathologic stage 1 cancer at time of diagnosis (a not unreasonable estimate), the difference in patient survival between conventional radical mastectomy and extended radical mastectomy with wide *en bloc* excision of skin and soft tissues would be in the order of 5,000 cases at the five year survival point."

The major deterrents to cure by *en bloc* operations are the circulating cancer cell [*38,39*] and early lymphatic extensions of cancer which exceed the boundaries of the *en bloc* operation. The superiority of extended operation in some stage 2 breast cancers is limited by the lymphatic extension factor. There is good rationale for the exploration of extended radical *en bloc* operations [*17,18*] even to the extent practiced by Margottini of Rome (who advocates superradical mastectomy plus monobloc excision of parasternal nodes and second stage supraclavicular dissection). Margottini cites a 14 per cent higher survival rate as compared to that resulting from the classical operation. So far as the circulating cancer cell is concerned, "the problem of the fate of the freely circulating cancer cell is like that of the fly in wintertime" [*40*]. Some possible advantage may result with increased survival time from adjunctive chemotherapy in supplementation of an extensive *en bloc* operation that satisfies Halstedian criteria of surgery for breast cancer. Explorations in these directions are warranted provided more emphasis is placed on the conceptual and technical requirements of the definitive *en bloc* operation.

There is conclusive evidence that the magnitude of the *en bloc* operation is a critical factor in the prognosis for survival, as well as are the determinant factors of biologic individuality of the tumor and the limits of extension of the cancer at the time of diagnosis and treatment. The most productive areas of basic research and clinical study will be concerned with a biologic test of curability [*43*], a molecular basis for therapy that is cancer cell specific, and new and increasingly subtle and effective ways of modifying host resistance to tumor. But these are the surgical conquests of the future. The most immediate and predictable improvement in the prognosis for survival of the patient with breast cancer would follow from the more general acceptance of extended radical mastectomy with wide *en bloc* excision of skin and soft tissues.

CONCLUSIONS

A definitive clinical study has been presented, based on a retrospective analysis of patients with operable breast cancer treated at the University of Oregon Medical School Hospitals and Clinics during the period 1940 to 1955 by *en bloc* operations of variable magnitude.

A comparison study was made of the results of treatment in terms of local recurrence and prognosis for survival.

The superiority of well conceived and well executed *en bloc* cancer operations on the principles laid down by Halsted three quarters of a century ago have been reaffirmed.

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DISCUSSION

CHARLES E. MACMAHON (Seattle, Wash.): In opening the discussion on this always intriguing problem, I must state that I have a congenital distrust of straining statistical methods in evaluation of the surgical approach to any disease. This is particularly true of the subject at hand in that each cancer and each host is a complex variable. In any individual instance it is impossible to tell with accuracy how important a specific therapeutic maneuver might be on either survival or in the detection of regionary persistence of the disease. When a less primitive approach to breast cancer is available (and it will have to be a nonsurgical approach to be less primitive), it will be as obvious that rational treatment is at hand as it was when penicillin was applied to the treatment of pneumococcus type 1, lobar pneumonia. In the original report of Halsted it is important to note that his primary objective was the local control of disease, and it is obvious that this too, is Dr. Peterson's primary objective. Only as long as the disease is within reasonable reach of an *en bloc* dissection does the surgeon have any hope of success. Once the local site has been abandoned and metastatic emissaries have been sent forth to do their systemic damage a surgical approach to breast cancer is as little rational as the surgical approach to chickenpox.

Certainly this statistical appraisal has emphasized that regionary persistence of the disease can be lessened by the application of procedure clearly outlined by Halsted in his original paper published in the Johns Hopkins Hospital reports in 1894. Certainly Dr. Peterson has carefully applied these principles of sixty-seven years standing to statistically good effect. I am certain, however, that he would be the last to deny that many of what seemed to be successful cases due to procedure were, in truth, successes due to low biologic potential of the tumors and to varying degrees of host resistance, rather than to the success of a specific surgical method.

In the large group of patients surveyed and so carefully analyzed, it would be ridiculous to argue that more careless methods could conceivably give this low incidence of regional evidence of persistent cancer. Certainly Halsted originally pointed out

that this wide, local incision did not increase either the surgical mortality or morbidity, and until better methods are at hand, it would probably be well to follow the careful directions laid down by Halsted and now re-emphasized by Dr. Peterson.

In evaluating what seems to be a regionary persistence of cancer of the skin, however, it must be emphasized, as pointed out by William Crawford White in an extensive study of problems of local recurrence after radical mastectomy for carcinoma, published in *Surgery*, January 1946, that for the surgeon to consider a recurrence as a reflexion on this lack of thoroughness in radicalism may not be so. This seeming persistence of the malignant process in the skin may well represent a direct cutaneous extension from subjacent intercostal and internal mammary nodes.

With the passage of sixty-seven years little has been done to clarify our understanding of this disease or any true improvement in surgical approach. It is entirely possible that we may rest here several decades until some technologic breakthrough makes this painstaking and yet crude approach to a fine biologic process unnecessary.

Lawrence B. Kiriluk (Seattle, Washington): Everything that Dr. Peterson has said this afternoon I would have to agree with. He has done a lot of work on this subject and his statistical analysis can't be denied. Also, I am not qualified to argue regarding the chi factor in evaluating the validity of his statistics.

I would like to comment on local recurrence. I noticed that in his slide on local recurrence, Dr. Peterson included recurrence at the internal mammary level as well as the axillary level but omitted the superclavicular level. I would like to limit my remarks to the skin recurrences as an indicator for evaluating some of these procedures.

He mentioned two factors which I think are very important in the influence of recurrence of carcinoma of the breast. The first was the density of the axillary metastasis and the second was the extent of the excision of the skin in the subcuticular tissue.

As to the first, the density of axillary metastases, I will certainly agree with this concept. I think you are all aware of the fact that essentially one-half of the patients who have axillary metastases from carcinoma of the breast also have at the same time metastases to the internal mammary nodes. This, then, to me would mean that the tissue between the internal mammary nodes and the tissue of the axillary nodes has a potential for being involved with cancer cells or at least exposed to them, and therein lies the possibility for recurrence.

In excision of the skin and subcuticular tissue I wasn't quite certain as to how wide or how thin the flaps were beyond the excision he showed. I presume it was to the midline as we all do it. One would have to assume that in performing a thicker excision of this area, which would include the subcuticular tissue and leave no skin overlying it, that there would be much less chance of disruption of the lymphatics and thus probably less seeding of tumor cells to the area which would ordinarily be left under thin skin flaps as they are produced.

I think that most of you will remember when Dr. William Hutchinson presented a paper to this Society four years ago on internal mammary node dissection. Actually, it was an internal mammary node biopsy that we had been doing over a period of six years, and during the last three years we thought this might be a guide for us as to whether we should perform simple or radical mastectomy. In those cases in which the internal mammary node biopsies were positive we performed simple mastectomies, and when they were negative, we performed radical mastectomies.

As you will remember, the rate for local recurrence among the patients with explored internal mammary nodes, as compared to a similar group of patients which had not been submitted to internal mammary node biopsy, was significantly higher and thus precluded our undertaking any further such procedures.

Also, in creating thin skin flaps, and I am sure there are many factors influencing the recurrence and growth of these cells in this area, the thought arises of the possibility of tissue devitalization and therefore tissue anoxia. In the process of creating large wide thin flaps, we may also be setting up a potential field or an artificial environment in which these cells "take," whether on the basis of anoxia or something else. Also, I think there are several other body areas in which there is a similar recurrence.

For instance, four or five years ago the Mayo Clinic presented a series of cases of recurrent carcinoma of the colon. In the majority of those cases, despite the fact that there were distant metastases, there was local recurrence at the suture line; the reason may be suture implantation, but there may also be other factors, such as tissue anoxia.

Also, in a review of carcinomas of the lung, we noticed that 69 per cent of these occur in the upper lobes although they are the smallest area of the lung field. It has been suggested that the reason the tubercular patient has lesions in the apex of the lung is probably because of the lower oxygen tension in that region. This may or may not have anything to do with this subject.

Dr. Peterson has made an excellent presentation of the cases in his series; however, the question arose in my mind as to what percentage of cases are we talking about. My impression, and this may create some discussion, has always been that in carcinoma of the breast, if we limit our discussion to simple versus radical versus extended radical surgery, fifty cases out of a hundred are not going

to be influenced very much in the long run as to which procedure we use. I think, likewise, that thirty cases are going to do well regardless of whether we perform a simple, extended radical, or routine Halsted radical. So now we are talking about 20 per cent of the carcinomas of the breast. Also, at each end of the range of this 20 per cent there will be some that will be influenced for better or worse, so we are further limited to probably talking here about 10 per cent of the cases.

HERBERT WILLY MEYER (Rancho Santa Fe, Calif.): This subject has been of especial interest to me throughout my surgical career. I would like to compliment Dr. Kountz on the excellent presentation of his fine work. I would like to also say to Dr. Peterson that I have been tremendously interested in what he has done and the careful study he and his associates at Portland have made of their cases.

I think it is fine that he showed the photograph of William Halsted, because it was William Halsted and Willy Meyer of New York who taught the principles of good cancer surgery of the breast in those years. Good cancer surgery means the removal of the primary lesion together with the lymphatic drainage area, in continuity whenever feasible.

We all know that besides lymphatic spread, there is also, unfortunately, spread by way of the blood stream in a certain number of cases in all types of cancer. I am certain that many of you saw the outstanding exhibit and demonstration by Dr. Warren Cole on this subject at the recent meeting of The American College of Surgeons here in San Francisco last October. The exhibit covered the question of the dissemination of cancer and the methods of its prevention; especially in carcinoma of the breast is this a very important point.

It was in the early 1890's that Halsted and Willy Meyer, realizing this fact, urged that there always be a wide excision of the skin of the breast and also that there be a most careful and meticulous dissection of the axilla. Willy Meyer, in those years, advised the early dissection of the axilla at the time of operation. He believed that one might help to prevent the dissemination of the cancer cells into the blood stream by ligating and dividing the blood vessels as well as the lymphatic channels early during the operation in the area of the axilla. Therefore, in the technic that he advised, besides the total removal of both pectoralis major and minor muscles, he dissected the axilla at the beginning of the operation. Dr. William Halsted, on the other hand, began the operation at the sternum, dissected across the chest wall and performed the dissection of the axilla later during the operation. The basic principles of the operations, however, were identically the same.

In good cancer surgery technic we must try to prevent all possible dissemination to the best of our ability. There are certain procedures, which Dr. Warren Cole has brought out so excellently, which my chief, the late Dr. George Semken, began to teach in 1910 at the old New York Skin and Cancer Hospital in New York City. In our clinic in New York we have followed these teachings up to the present time. They include the various procedures for the prevention of spread of the disease, especially before the time of operation. By that I mean at the time of physical examinations. Here the most vital consideration is gentleness—gentleness in the examination of the breast. The same applies to the teaching of self-examination by our patients. At the time of operation the same gentleness is vital in the preparation of the operative field. There is always the danger of breaking off some cancer cells from a tumor thrombus in a vein within the tumor by rough handling of the breast or too great pressure in the preparation of the breast. These cells then become a tumor embolus and spread quickly to different distant parts of the body.

Then there is the question of invasion by the cancer. Warren Cole has used a term which I think is most excellent. It is the question of intravasation of tumor cells into blood vessels. If the growth and activity of the tumor is such and if the tumor is close to a vein and if the pressure against the vein is greater than the pressure within the vein then the cancer cells may enter the lumen of the vein by intravasation. This point is also important in the performance of a biopsy. In our clinic we never did a breast biopsy under local anesthesia except in those few circumstances in which general anesthesia was contraindicated. This practice was followed in order not to increase the pressures in the area of tumor by infiltration of local anesthesia and thereby bring about intravasation.

Finally there is the matter of implantation. This danger can be avoided to a large extent by what we call "cancer surgery technic." I do not have the time here to explain the details of this technic; however, it is extremely important during the operation to do everything in cancer surgery that will prevent implantation of cancer cells in the surgical field. So far as local recurrence and its prevention is concerned, from the 1890's on Willy Meyer and, I believe, Halsted also, irrigated the wound at the end of the operation. They employed Ringer's or saline solution. Recently Warren Cole has suggested 0.5 per cent buffered hypochlorite solution, because cancer cells free in the wound can thereby possibly be destroyed. Moore, of the Roswell Park Memorial Hospital in Buffalo, has recently also advised the use of chemotherapy at the time of operation and thereafter. This has apparently been of real value.

All of these procedures, therefore, are of great importance. I am not as fearful of the matter of local reappearance in the field of operation, even in the presence of node metastases, as I am of the distant metastases that may already be present in microscopic form at the time of operation and which up to this time we cannot diagnose early enough. These distant metastases so often undo the good of an efficient, adequate radical operation.

IAN MACDONALD (Los Angeles, Calif.): I am confused, interested and fascinated by all of this. You remember, those of you who read his writings thoroughly, that Haagensen, the gentleman of the thin skin flaps and the five hour procedure, has a 12 per cent plus local recurrence rate. Down in the Pueblo of Los Angeles my associates and I, the last time we reviewed this subject, in almost 400 radical mastectomies, had a local recurrence rate after five years or more of 5.7 per cent. We have been doing nothing but what I thought all these years was a Halstedian operation.

Personally, I seldom skin graft because I prefer the skin that the Lord put there. In short, I use sliding flaps generously and do not graft more than one in twenty, but I think the amount of skin I remove is commendable in ordinary circles.

As I hear about more intensive attacks on mammary carcinomas, I am impressed by the fact that the better results from them are during the first decade of follow-up. I think Jerry Urban's final figures will reveal that his even more ambitious intrathoracic attack is going to produce superior results only up to ten years. The results from Portland show that at and after ten years, apparently, the more aggressively treated and those treated by the standard approach are surviving at the same rate, if I have interpreted those curves correctly.

I have had a bit of education on statistics only as a bystander trying to become initiated, and I have been told by experts with whom I have worked that in biologic problems, such as breast cancer, a P value of less than .01 is desirable for the expression "highly significant"; that values in the order of less than .025 are possibly significant but not necessarily so.

Finally, I wonder whether or not the subgroups that have developed in these 204 cases are of such reduced sample size that the statistical survey loses some of its apparent validity.

Haagensen's improved results were derived by selection, not from the five hour procedure.

Urologic Aspects of the Alternating Urachal Sinus

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THE urachus, although entirely derived from the fetal bladder, has a direct connection with the umbilicus, occasionally even after fetal life. It thus lies between the fields of urology and general surgery. In a total of eighteen cases of urachal disorders, we have performed the necessary diagnostic steps upon and have treated four patients with alternating urachal sinus, a disorder which produces both umbilical drainage and vesical inflammation [5].

FACTORS PERMITTING ALTERNATING UMBILICAL AND VESICAL DRAINAGE

The urachus is derived from the narrowed apex of the bladder. Although attached to the umbilicus before birth by its connection with the allantois (Fig. 1), it is drawn down by the descent of the bladder and in the adult becomes an appendage about 5 cm. long on the vesical apex [4]. (Fig. 2.) However, in extensive dissections, Hammond and coworkers [3] determined that there are some persons in whom the urachus extends to the umbilicus, for an average length of 12 cm. It is from within this group that patients come with the disorder of alternating urachal sinus.

The urachus retains its lumen in an attenuated form [6] and is filled with desquamated debris. In a third of the disssections, a communication between the urachus and bladder could be demonstrated [1,7], but it was always minute.

The pertinent findings from these previous

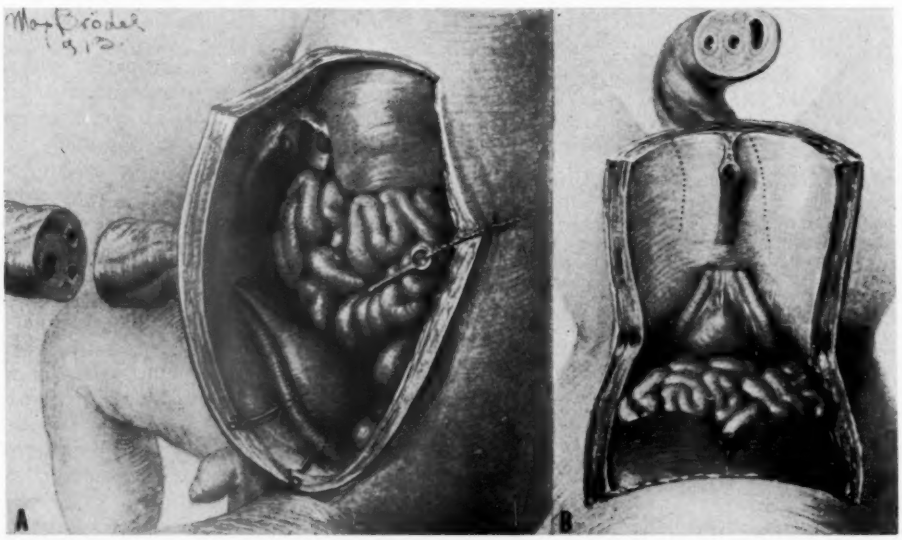

FIG. 1. Six to seven month old fetus. Lateral (A) and posterior (B) views of umbilical region showing apex of bladder extending to umbilicus between umbilical arteries. (From: CULLEN, T. S. [2] Fig. 29.)

FIG. 2. Adult. Posterior view of umbilical region showing obliterated umbilical (hypogastric) arteries and urachus, usually 5 to 7 cm. long to extend half-way to umbilicus. (From: CULLEN, T. S. [2] Fig. 37.)

studies may be summarized as follows: The urachus (1) is derived from the bladder, (2) may occasionally keep its umbilical connection, and (3) retains its lumen.

OTHER EFFECTS OF URACHAL ABNORMALITY

To place the disorder under discussion in proper relation, other urachal abnormalities are merely enumerated here:

FIG. 3. Case 1. Cystogram showing ureteral catheter which was inserted into the urachal sinus through the umbilicus but did not enter the bladder. Typically, no dye enters the sinus from the bladder.

1. If the urachus remains patent or the apex of the bladder fails to form a urachus, a urinary fistula will be observed at birth (congenital patent urachus, "completely open").

2. The urachus may remain patent only at its vesical termination, and form a vermiform appendage on the bladder dome (vesicourachal diverticulum, "open internal").

3. The inner end of the urachus may close, but the subumbilical portion remains open (umbilical cyst and sinus, "open external").

4. The last group, the subject of the present discussion, is composed of patients in whom both ends of the urachus are potentially patent. Infection then can extend centrally to the bladder, peripherally to the umbilicus or to both areas simultaneously (alternating urachal sinus, "alternating open"). This group has received the least attention in previous reports, yet provides the most interesting subjects for diagnosis and treatment.

TABLE I
SIGNS AND SYMPTOMS

Case No. and Sex	Age at Onset (yr.)	Initial Symptoms	Age at Examination (yr.)	Umbilical Symptoms	Urinary Symptoms
1,F	1	Umbilical "erysipelas"	2	At 1 yr. of age swelling, irritation, foul discharge present; spontaneously subsided	At 2 yr. of age frequency, fever, Escherichia coli infection, followed in four weeks by umbilical abscess
2,F	17	Periumbilical pain with discharge	18	Slight umbilical tenderness	Frequency, urgency, nocturia
3,M	21	Umbilical discharge	22	Onset with periumbilical pain	Soon followed by urinary urgency
4,F	22	Nausea, "cystitis," fever	22	None, palpable mass	Urgency, frequency, fever

SYNDROME OF ALTERNATING URACHAL SINUS

The incidence of the disorder is much greater in adults. (Table I.) Our one case in childhood is a rarity. The patient does not have umbilical disturbance at birth and has a long period free of symptoms. Periumbilical tenderness commonly occurred at the onset, but evidence of urinary tract infection usually appeared simultaneously, with symptoms such as urinary frequency and urgency, fever and even renal symptoms. The exception appeared in one patient (Case 1), in whom there was an interval of one year between the umbilical and urinary symptoms. The periumbilical inflammation became so fluctuant in one patient (Case 1) that it necessitated incision and drainage.

DIAGNOSIS

Examination usually revealed redness of the umbilicus, often with inflammatory changes in the skin. (Table II.) The entire periumbilical area was tender. In two patients (Cases I and III) a probe or ureteral catheter could be insinuated down the umbilical sinus. (Fig. 3.) It passed as far as 8 cm. in one patient and produced a desire to void, indicating that it had made contact with the bladder.

Cystograms failed to reveal a tract extending from the bladder in any of the patients. (Fig. 3.) This is in contrast to the roentgenographic appearance of congenital patent urachus or vesicourachal diverticulum, in which filling of the urachus is seen. Cystoscopy

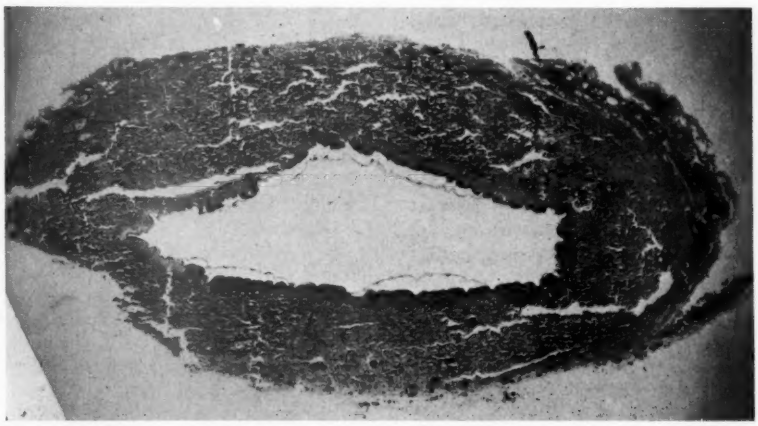

FIG. 4. Microscopic section (Case III) through excised urachal sinus showing transitional epithelial lining surrounded by scarred smooth muscle.

TABLE II
DIAGNOSIS AND TREATMENT

Case No. and Sex	Cystogram	Cystoscopy	Treatment	Result
1,F	No communication	Scar and tenting on dome	Drainage of "abscess" and excision of urachus	Cured
2,F	...	6 cm. bulge at dome	Excision of urachus	Cured
3,M	No communication	...	Excision of urachus	Cured
4,F	...	Red polyp on dome	Excision of urachus	Cured

showed no openings into the urachus in any case. In one patient (Case I) a scarred area was associated with tenting of the dome; in a second (Case II) a bulge measuring 6 cm. protruded into the bladder from the dome; and in a third patient (Case IV) a red polyp was apparent at the apex. Figure 4 shows microscopic section of excised urachal sinus (Case III).

TREATMENT

Dissection may be facilitated by injection of methylene blue into the tract and insertion of a balloon catheter into the bladder. A midline incision, usually designed to enable excision of the umbilicus, is extended almost to the symphysis. Excision is performed from above downward.

During one operation (Case I) it was necessary to lay the tract open with a grooved director because of extensive scarring; in this and in two other operations, excision of the underlying peritoneum was required, for the same reason.

The tracts were resected into the muscular coats of the bladder, but were excised without the necessity of opening into this organ. The vesical wall was imbricated with catgut sutures and a small drain placed extraperitoneally to this area. The rectus fascia was reapproximated after the peritoneum had been closed. Chromic catgut sutures were used because of the possibility of urinary drainage. Stay sutures may be advisable since the tract is infected.

The subsequent course of these four patients gave no evidence of further trouble.

SUMMARY AND CONCLUSIONS

1. In a small proportion of apparently normal persons, the urachus may remain attached at the umbilicus. Since a potential lumen normally persists throughout adult life, infection in the desquamated debris within the urachus may spread in these cases in both directions, appearing at the umbilicus and in the bladder.

2. The syndrome of the alternating urachal sinus consists of periumbilical symptoms followed sooner or later by evidence of vesical irritation. Four patients have been studied and treated.

3. The diagnosis is made by inserting a probe into the sinus and by visualizing a lesion on the dome of the bladder by cystoscopy. Cystography has not revealed the tract.

4. Curative treatment is excision of the entire urachus.

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DISCUSSION

EDWIN G. CLAUSEN (Oakland, Calif.): I think all of you realize that this condition is actually quite rare and many reports are of single cases. Most of these cysts developed in adults, although we have had two at the Children's Hospital of the East Bay.

The first patient did not have any urinary tract symptoms. The child merely had recurrent abdominal pain, fever of undetermined origin, failure to gain weight and general malaise. The urologic as well as the gastrointestinal tract were studied. Finally an exploratory laparotomy was performed and a large urachal cyst found. Following excision of the cyst the patient became asymptomatic.

The second case was more intriguing and was associated with urologic symptoms. A two and a

half-year-old child had had recurrent attacks of cystitis for about a year. The child had been studied completely and was found to have a normal upper urinary tract and bladder and no obstruction of the lower urinary tract.

On one hospital admission the patient again underwent cystoscopy, and at the dome of the bladder some edema was found. Signs of inflammation occurred at the umbilical region. Following incision and drainage of an abscess in this area it was apparent that an infected urachal cyst was present, which undoubtedly had been showering organisms into the bladder. Following incision and drainage of the inflammatory process a secondary operation was performed with excision of the cyst, and the patient was completely cured.

We had actually ten patients with urachal disorders, but only two of these that had an internal cyst.

FRANK HINMAN, JR. (closing): We have had only eighteen cases of urachal abnormalities in the last fourteen years at U. C. Hospital, of which four fitted into this group. These eighteen obviously are too disparate to discuss in detail, and therefore this particular group was selected. The other types are either easily noticed at birth or are definitely umbilical. Only the four discussed herein were both umbilical and urologic problems.

A Successful Case of Homotransplantation of the Kidney Between Identical Twins

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THE FIRST successful case of homotransplantation of the kidney between identical twins was reported by Merrill et al. [2] in 1956. Since that time, a modest number of cases have been reported in the literature. The historical literature on kidney transplantation has been described by Hume [1]. In this scholarly article, he classified the transplants between identical twins as isotransplants in order to distinguish the results from those of true homotransplants in which the antigenic mosaic is not identical. The following represents a case of isotransplantation.

CASE REPORT

CASE 1. L. P., a forty-seven year old white man, was referred to the Stanford Medical Center on July 7, 1960, for evaluation of his renal status. The patient's history revealed that at seventeen years of age, he complained of "kidney trouble" and pain in his back. A tonsillectomy and an adenoidectomy were performed. In 1943, his right kidney was removed because of a stricture of the ureter which was congenital in origin. Following

FIG. 1. Pyelogram on L. P. (August 11, 1957) showing moderate hydronephrosis and kidney size. (See Figure 2 for comparison.)

FIG. 2. Attempted pyelogram (April 1960) on L. P. Failure of kidney to concentrate. Kidney shadow shrunken.

surgery, he had several bouts of fever and pain in his left flank for which he was treated by catherization and irrigation of his left kidney.

In 1956, his present physician first saw him. A diagnosis of chronic pyelonephritis was made on the basis of the changes of the intravenous pyelogram.

At this time, the blood urea nitrogen was 22.2 per cent and creatinine was 1.7 mg. per cent. The patient was hospitalized in 1959 because of an injury to his back. Between 1956 and 1959 his systolic blood pressure stayed below 150 mm. Hg. The blood urea nitrogen was 25.8 mg. per cent, at this time. Determinations for sodium, phosphorus, calcium, potassium and chlorides were said to be normal. The patient was hospitalized for a third time in April 1960. Data recorded showed the blood urea nitrogen was 124.5 mg. per cent and creatinine 7.32 mg. per cent, sodium 145 mEq. per L., potassium 4.4 mEq. per L., CO_2 15.6 mEq. per L. and chlorides 102.9 mEq. per L. On treatment with intravenous fluids he improved according to clinical criteria and chemical measurements. On June 11, 1960, he experienced an episode of left ventricular failure. His blood pressure was 200/110 mm. Hg.

Following this episode, he was referred to the Stanford Medical Center. Physical examination revealed his blood pressure was 195/115 mm. Hg, his weight 62.1 kg. and height 177 cm. He was undernourished and sallow in appearance. Scars indicating a right nephrectomy and an appendectomy were apparent. No other abnormal physical findings were noted.

Results of urinalysis were as follows: specific gravity, 1.007; 2 plus protein, with a few hyaline casts; packed cell volume 26 per cent; hemoglobin 8.5 gm. per cent; red blood cell count 3,120 per cu. mm.; white blood cell count 7,500 per cu. mm.; creatinine 13 mg. per cent; blood urea nitrogen 99 mg. per cent; chlorides 103 mEq. per L.; CO_2 22.1 mEq. per L.; potassium 4.8 mEq. per L.; and sodium 138 mEq. per L. Urine culture revealed 350 colonies of Proteus per cc. An x-ray film of the abdomen showed that the outline of the left renal shadow had shrunk perceptibly in comparison to the film taken in August 1957. (Figs. 1 and 2.)

It was during this examination period that the patient volunteered the information that he was an identical twin. The patient's mother remembered clearly that there was only one after-birth. The twin brother was contacted and he agreed to donate a kidney.

Accordingly, on July 20, 1960, a full thickness skin graft was exchanged on the forearms of the brothers under local anaesthesia. The grafts healed well and assumed the qualities of the surrounding skin. The following blood groupings were performed:

FIG. 3. Normal intravenous pyelogram on K. P.

	B	c	C	E	e	M	N	Kell	Fy^a
Brother K.	+	+	−	+	+	+	+	−	−
Patient L.	+	+	−	+	+	+	+	−	−

An intravenous pyelogram of the healthy twin showed normal kidneys. (Fig. 3.) An intravenous aortagram showed that the right renal artery was the larger of the two. The twin's urine culture was sterile.

Meanwhile, in spite of medical therapy, the patient regressed. On readmission to the hospital August 17, 1960, his blood urea nitrogen was 170 mg. per cent. Ten days later, the artificial kidney was placed in the patient with considerable immediate improvement. On August 29, 1960, he again had pulmonary edema with severe hypertension. His blood pressure was impossible to control with drugs. On August 30, 1960, his condition was such that we felt impelled to proceed with the transplant even though the skin grafts were now forty-one days in place.

A nephrectomy was performed on the healthy twin by Dr. Oberhelman. With the patient under general anaesthesia in the lateral position, the right flank was opened through a curved incision below the twelfth rib. The kidney was separated from the surrounding fat, allowing identification of the renal arteries, the vein and ureter. After maximum length had been obtained on each structure, intravenous heparinization (2 mg./kg.) was instituted ten minutes before clamping the renal artery. After clamping, the kidney was

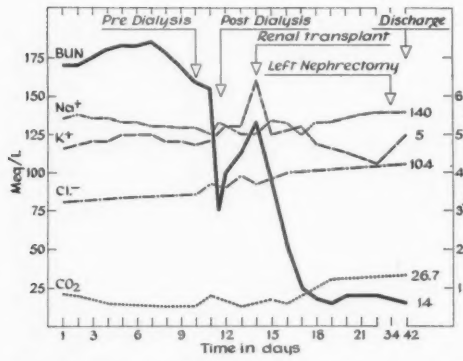

FIG. 4. Graph showing changes in electrolytes during hospital stay. Note effects on blood urea nitrogen of dialysis and transplant.

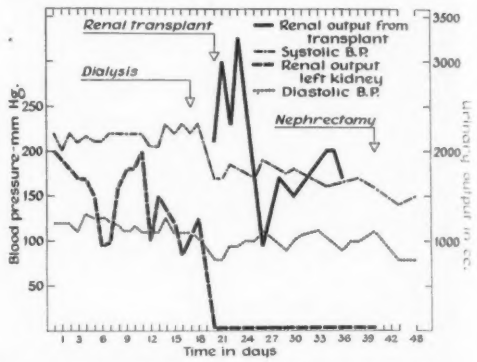

FIG. 5. Graph showing urinary volume and blood pressure fall during hospital stay.

rapidly removed and sent to the second operating room. The heparin was neutralized with Polybrene.® The wound then was closed in layers. The patient withstood the operation without difficulty.

The transplantation of the kidney was performed by Dr. Cohn. Under continuous spinal anaesthesia, a wide supra pubic transverse incision was made freeing the rectus muscles from the pubis. Dissecting retroperitoneally, the structures in the right side of the pelvis were identified. The hypogastric artery was dissected out to its first branching, and cut. This left a stump of the hypogastric artery, 3 cm. in length and about 4 mm. in diameter. Next the iliac vein was exposed. At this time the donated kidney was delivered. After cleaning and stretching the renal artery, it was anastomosed to the end of the hypogastric artery. The renal vein was anastomosed next to the side of the iliac vein. No. 5–0 silk sutures were used. The clamps on the vessels were removed; the time of vascular anastomoses was twenty-two minutes. Urine appeared in gushes at once and continued from that time. Because of the Proteus infection in the urine, the left ureter was freed and cutoff at its junction with the bladder. The proximal end was brought out through a left flank stab wound. A small hole was then made into the bladder and the right ureter anastomosed to the bladder mucosa with interrupted No. 5–0 silk sutures in two layers. The abdominal wall was then reconstructed with pelvic drainage. Data are summarized in Figures 4 and 5.

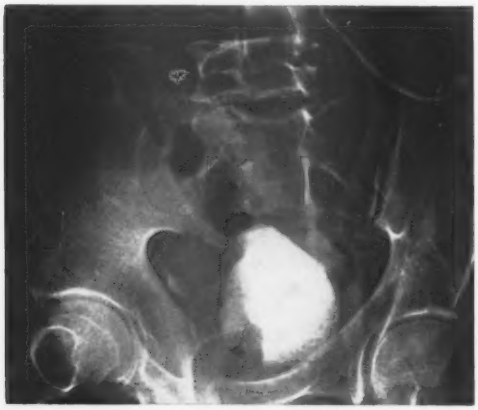

FIG. 6. Postoperative intravenous pyelogram showing rapid emptying of pelvic kidney indenting the bladder.

In the immediate postoperative period, the patient produced large volumes of urine from the transplanted kidney. (Fig. 6.) His blood pressure remained at 170/100 mm. Hg, a fall from its previous high level. The left kidney put out 3 to 6 cc. of water a day. An attempt to correct the anemia with a transfusion was halted because of a rise in blood pressure following administration of 250 cc. blood. On September 9, 1960, because of increasing tenderness in the left flank and our fear that this finding meant the flare-up of the Proteus infection in the left kidney, this kidney was removed (Dr. Cohn). The operative procedure was notable only in that the kidney was adherent to its surrounding tissues and that three small arteries made-up the arterial supply.

Pathologic examination of the kidney showed the kidney to be 10 by 5 by 4 cm. and weighing 105 gm. There was almost total destruction of the renal parenchyma by chronic pyelonephritis. (Fig. 7.) In addition to the chronic component, there were numerous small abscesses present. This inflammatory component involved the renal pelvis and the ureter. The arteries of the kidneys had been obliterated by intimal proliferation. The diagnosis was marked chronic and acute pyelonephritis.

Following nephrectomy of the left kidney, the patient continued to improve slowly. His blood

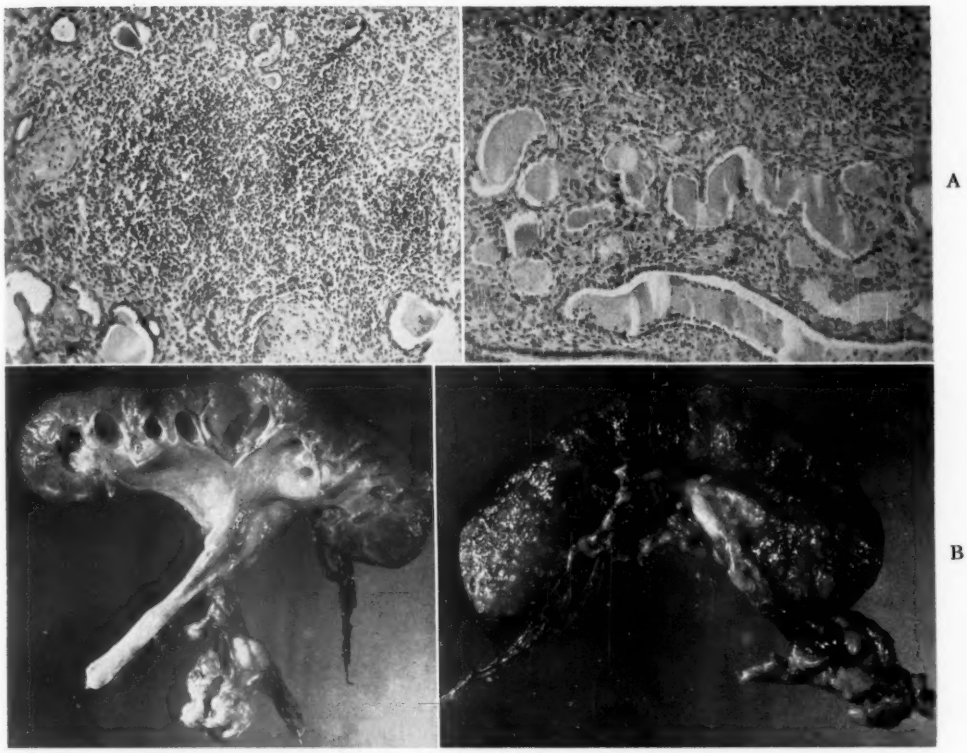

FIG. 7. A and B, microscopic and gross pictures of the remaining diseased kidney, showing scarring, infiltration of cells and obliteration of normal architecture of the kidney.

pressure slowly fell; on discharge from the hospital it averaged 145/90 mm. Hg. He was discharged on the thirty-second hospital day. An intravenous pyelogram obtained six months postoperatively is shown in Figure 8.

COMMENTS

From the technical point of view, the problems presented in this case were no different than those in previously reported cases. We believed that it was simpler to induce heparinization in the donor rather than in the transplanted kidney alone, but, of course, we cannot prove that the immediate and continued satisfactory function was directly related to this maneuver.

As has been noted by others, renal nerves are apparently not necessary for renal response to diversified functions. Attention is called to the use of the aortagram as a source of important organization concerning size and number of renal arteries.

The nucleus of the medical problem preoperatively was the treatment of congestive heart failure and far advanced renal insuffi-

FIG. 8. Intravenous pyelogram six months postoperatively.

ciency. The etiology of the congestive heart failure was in a large part due to the severe hypertension. It was impossible to control the hypertension properly by medical measures, and, after two attacks of acute pulmonary edema, we believed it imperative to proceed with the transplant even though the original plan had included at least two more dialyses. Even though, in most cases, diseased kidneys remain in the recipients at the time of transplantation, there usually is an immediate fall in blood pressure when the transplanted kidney begins to function. This observation was noted in the present case, and was probably the deciding factor in the immediate survival of the patient. Following removal of the diseased left kidney, there was a further reduction in blood pressure.

Creatinine clearance was measured on the eleventh postoperative day, and was approximately 50 per cent of the creatinine clearance value of the donor before nephrectomy.

The prognosis of this patient should be good for the following reasons: (1) severe hypertension has only been present about one year; and (2) the underlying pathologic process was infection, thus the transplant is unlikely to develop disease as has been true in some of the patients in whom glomerulonephritis was the cause of renal failure.

At the present time the patient is asymptomatic. His urine cultures continue to remain heavily contaminated with Pseudomonas.

SUMMARY

1. A case of successful homotransplantation of the kidney between identical twins is reported.

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DISCUSSION

Joshua Lederberg (Stanford, Calif.): Dr. Lederberg reviewed the problem of tissue compatibility from a genetic standpoint, and discussed recent theories of the genetic and cell-biologic basis of the immune response.*

Allan D. McKenzie (Vancouver, B. C.): Dr. Cohn has given us a modest understatement of a considerable feat, and I speak from a little knowledge for I had an experience of an identical twin situation in September 1960.

A thirty-seven year old lumberjack, who had been known to have trouble with his kidneys for some years, was brought into the hospital *in extremis*. A friend, having read in a popular magazine about kidney transplantations, wished to offer a kidney. When it was explained that this was possible only between identical twins, it turned out that the patient did indeed have an identical twin in the community.

Dr. Cohn's understatement thus becomes apparent. We decided to call together those people who might be involved in preparing the way to see if the transplantation was possible. The people entailed included urologists, plastic surgeons, two other general surgeons; the nursing staff and the director of the chemistry laboratory. We also included the people from the blood bank, both the Red Cross and the hospital banks, persons to give medicolegal advice and representatives of the hospital administrative staff. In addition, we included a geneticist, a dentist and a police fingerprint expert.

On improvement with dialysis and with the preliminary opinion that they were monozygotic twins, we exchanged grafts and continued dialysis. The fifth and best dialysis ended in a cardiac arrest and death of our potential recipient.

A difficult decision was thereby averted, for our donor was not quite perfect; he had an elevated blood sugar and a glucose tolerance curve of the latent diabetic type. Would we have been justified in taking a kidney from a latent diabetic and transplanting it to save the life of his twin?

I would like to ask Dr. Cohn what he believes the prognosis is for his patient? In some such patients, complications have developed in the transplanted kidney.

Willard E. Goodwin (Los Angeles, Calif.): Renal homotransplantation is my greatest interest. A couple of years ago, I spent my sabbatical year working on this problem: first, in Boston at the Peter Bent Brigham Hospital with Dr. Joseph Murray and subsequently in Edinburgh with Professor Michael Woodruff.

The problem of renal transplantation between identical twins should be put a little bit into focus. This is the first kidney transplantation between twins performed in California and is probably the second on the Pacific Coast. About twenty-five

* Lederberg, J. Genes and antibodies. *Science*, 129: 1649, 1959.

such cases of renal transplantation between identical twins have been performed *en toto*. Most of the operations were performed in Boston by the Brigham group. Others have been accomplished in Montreal, New Orleans, Richmond, Kansas City, Edinburgh and Portland. I hope that Dr. Dunphy can be persuaded to tell us about the Portland case, which has certain unique facets.

Renal transplantation between identical twins, first performed successfully at the Peter Bent Brigham Hospital in the fall of 1954 as an exciting clinical experiment, is now an accepted procedure, providing the indications are proper and the donor is able to give the kidney without jeopardizing his own life.

So far as age is concerned, there seems to be no barrier at either end of the line. The youngest patient to have this operation was twelve years old and the oldest is the one reported today by Cohn et al. One of the patients who had this operation while I was at Brigham was a forty-seven year old dentist. He also had a history of cancer of the thyroid gland which was thought to be cured. This history of malignancy did not stand in the way of a decision to do the transplantation.

There have been a few technical failures; this is a more serious potential problem in children than it is in adults. However, the technical aspects are well developed, and there should be no insurmountable problem in exchange of kidneys between identical twins.

As Dr. Lederberg has pointed out, the basic problem is that of homotransplantation from one person to another when the donor and recipient are not identical twins. As you well know, the inevitable rejection reaction is a formidable barrier to the use of organ transplantation outside the experimental laboratory.

In our own experience at The University of California at Los Angeles, we have had one renal homotransplantation between a mother and daughter. This was performed in September 1960 at the request of both mother and daughter. The homotransplanted kidney functioned for nearly five months and was still satisfactory when the patient died of uncontrolled pulmonary infection. She did not die of renal failure.

We believe that we learned something from this experience with human renal homotransplantation. The important lessons were the following: (1) consanguinity, which has been mentioned today, seemed to be important. In our patients, blood groupings were the same, with two minor exceptions, when tested for fourteen different factors. (2) We attempted to suppress, and I think did so, the white blood lymphocyte series with nitrogen mustard and later with the use of the drug Cytoxan.® We thought that this helped to delay the rejection reaction. (3) Renal capsulotomy is a technical factor which is not of major significance in auto- or isotransplantation of the kidney, but is important in homotransplantation. Transplanted kidneys do swell with edema after transplantation because their lymphatic drainage is temporarily destroyed by surgery. We believe that capsulotomy allows the kidney to survive an immediate postoperative period of serious edema. (4) Rejection in our case began about one month after transplantation. The next thing that we learned was that it was possible to stop this rejection by massive doses of adrenal corticosteroids (200 mg. a day of Prednisone, about the equivalent of 1,000 mg. of Cortisone). This stopped the rejection. We observed this twice and were quite sure of the response.

When our patient finally died, the terminal episode was due to pneumonia secondary to poor resistance to infection associated with use of steroids. The transplanted kidney was still functioning, although somewhat impaired.

Dr. Hume's experiments with animals show quite clearly that the use of x-ray therapy to prevent a renal homograft rejection in human beings is probably not feasible. The required doses of x-ray therapy are too great to be useful with safety. Even the kidney transplantation group at Brigham is beginning to come around to this point of view, and to get away from the use of x-ray therapy as an instrument to prevent the rejection reaction.

Most recently, various drugs have been employed elsewhere to try to prevent the rejection reaction. Six-Mercaptopurine has been used particularly on animals in the laboratories. The use of 6-Mercaptopurine seemed to prolong renal homotransplant survival in dogs. It was tried on three patients at Brigham, but all failed.

The most interesting thing along this line is a report from the meeting of the University Surgeons, published recently, in which Pierce and Varco from the University of Minnesota described survival of a homotransplanted kidney in a dog for 255 days with the use of 6-Mercaptopurine. This kidney was still functioning at the time the paper was presented. They proposed to stop the drug to see if perchance an adaptation might have occurred in the transplanted kidney.

As mentioned in discussions here today, the hope for the future of homotransplantation of organs is the hope of suppressing in some way the immunologic reaction which leads to rejection. Perhaps it is a "will-o'-the wisp," but if this could be carried out long enough so that some sort of an acquired tolerance could take place, in a way which we are not now capable of understanding, it is possible that homotransplantation of tissues and organs may become a surgical reality.

J. Englebert Dunphy (Portland, Ore.): I would like to tell you briefly about the patient

operated on at the University of Oregon by a team headed by Dr. Clarence Hodges. The West Coast has the distinction now of having performed transplants on the oldest and the youngest patients, our twins being only twelve years of age. One of the features of the larger series has been the disturbing point that the younger the patient, the more likely the development of disease, particularly glomerulonephritis, in the transplanted kidney.

For this reason, in relation to our patient, we seriously considered removing both kidneys prior to the transplantation, but for a number of reasons decided not to do it. The kidneys were removed during the immediate postoperative period.

The interesting point about the present state of the twins is that the sick twin has greatly exceeded the healthy twin in growth; and she is a larger, bigger and stronger girl at this time (over one year since transplantation) than her sister, which I think indicates that this kidney is functioning admirably.

In reference to Dr. Lederberg's speculation of the future, one cannot help hoping that, somehow, an organ specificity can be introduced into the immune reaction, because there certainly are organ differences. One can transplant collagen in a way that one cannot transplant skin, and one can transplant a parathyroid gland and have it behave in a much different fashion from a kidney. I hope that not only can we have a special cell reacting, but also we need a special antigen for picking out the cell. One can become quite optimistic even though the barriers are formidable.

ROY COHN (closing): We did cross match many blood groups in this case. We also did one other thing which I have not seen described in any of the other technical papers. We heparinized the donor, the whole donor, rather than just the kidney. It seemed like a simpler way to do it, rather than irrigating the kidney.

There has been mention of acquired tolerance and that aspect of the problem. There are many other interesting facets to this problem, one of which is what do the nerves of the kidney do? It does not seem to make any difference in renal function. This is a completely denervated kidney as far as urinary output and clearance of the various ions in the kidney, but the urine appeared to be normal. This will be a fruitful field for investigation, I am sure.

Scribner has described the insertion of an arteriovenous fistula in these chronic uremic patients who have to be dialysed many times. There is a plastic gadget which he puts into the artery and vein of the arm. We have utilized this procedure in one patient in whom we had a somewhat different problem. It works very well without heparinizing the patient, and one does not destroy all the patient's spare vessels.

BOOK REVIEWS

Prosthetic Valves for Cardiac Surgery. Edited by K. Alvin Merendino, M.D. 586 pages. Charles C Thomas. Springfield, 1961. *$8.25.*

This book is the collection of papers given under the auspices of the National Heart Institute in September of 1960. The publishers have given special attention to making the book available as soon as possible. This volume is the most up to date publication on recent advances in this exciting field of research. The entire gamut of problems is covered, beginning with physiology and including materials, designs and replacement methods. The contributors are not only in the medical profession but include engineering and fabrication personnel who have worked together to make the replacement of human valves by prosthetic material an accomplished fact.

This book is obviously a must for any surgeon dealing with cardiac valve replacement and, in addition, affords many fundamental studies on the mechanical and physiologic properties of material used for replacement of other human tissues. The book is a milestone in cardiac surgery and has served its purpose admirably, namely, to decrease unnecessary duplication in research and to show clearly the problems for future solution.

C. V. M.

Hospital Infection. By R. E. O. Williams, M.D., M.R.C.P., R. Blowers, M.D., L. P. Garrod, M.D., F.R.C.P. and R. A. Shooter, M.D. Yearbook Publishers, Inc. Chicago, 1960. *$7.50.*

The authors of this book have between them probably more than a century of experience in the field of hospital infections and the book they have written reflects this in that it is an exhaustive and level headed review of an extremely complex subject. It covers virtually every variant of hospital-acquired infection that has been described and outlines most of the known technics for investigation of these problems as they arise.

Those who are looking for specific and dogmatic opinions on a method for studying any particular problem are likely to be disappointed, but those who are interested in a very realistic and dispassionate review of both problems and solutions will benefit greatly from this most excellent book. It can be recommended with few reservations to anybody concerned with the problem of hospital-acquired infection, whether he or she be surgeon, nurse, bacteriologist or public health worker. It should be emphasized that this publication is greatly superior to anything else the reviewer has encountered in this field.

C. R. M.

Transactions of the Pacific Coast Obstetrical and Gynecological Society, Volume 27. 78 pages. Western Journal of Surgery Publishing Co. Seattle, 1959.

This volume contains the proceedings of the 26th annual meeting of the Pacific Coast Obstetrical and Gynecological Society and a list of the officers and members. It includes the complete text of eighteen articles on obstetric and gynecologic subjects presented at the scientific meeting.

Current Therapy—1961. Edited by Howard F. Conn, M.D. 806 pages. W. B. Saunders Co. Philadelphia. *$12.50.*

Current Therapy—1961 follows the same general outline as found in its twelve previous editions. This edition continues to successfully bring to the physician brief, up to date articles which reflect the current treatment of diseases as practiced by recognized medical authorities.

For the busy general physician this book would be most helpful in providing information concerning the use of newer drugs, their dosages, and side effects arising from their use. *Current Therapy* has been and remains an excellent reference.

D. L. K.

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